PROGRESS IN

Arthritis

Edited By

John H. Talbott, M.D.

And

L. Maxwell Lockie, M.D.



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Dedicated To The Memory Of

Stockton Kimball, M.D.

1902 - 1958

Dean of the University of Buffalo School of Medicine

1946 - 1958

A Brilliant Student

An Esteemed Physician

and

A Loyal Colleague

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Preface

THIS VOLUME is designed to present discussions by recognized authorities on selected subjects in the broad field of arthritis, rheumatism and connective tissue disorders. "Progress," in the sense implied, signifies a thorough, current evaluation of the individual subject material by the writer of the special chapter. We feel that the timeliness of such a book is underscored by the fact that within the span of our professional experience, the study and treatment of arthritis has been elevated from that of a poorly understood clinical subject to its present high state, in which it is the object of tremendous curiosity.

Innumerable forces and factors have contributed to this metamorphosis. The indefatigable zeal of Drs. Philip Hench, Russel Cecil, Walter Bauer, Ralph Boots and a few others has stimulated the pursuit of a more adequate understanding of various phases of this symptom complex. Without such leaders current progress would be far less impressive. The tremendous impact following the use of adrenocorticosteroids and ACTH has greatly accelerated and lent impetus to research in this extremely important area of medicine.

Another vital force responsible for progress in this field is the availability of funds for research and education. In 1957, the National Institute of Arthritis and Metabolic Diseases alone had a budget of more than 20 million dollars, a major portion of which was allocated for education and research in the field of arthritis and connective tissue disorders. The Arthritis and Rheumatism Foundation as well as other foundations, together with pharmaceutical manufacturing companies and interested private individuals, each has contributed toward the support of the investigators and clinicians who are now able to exploit to a maximum the isotopes, histochemistry, electromicroscopy, immuno-chemistry and enzymes, to mention a few of the related scientific tools currently available. "Progress in Arthritis" is not an all-inclusive volume as is the Rheumatism Reviews, published from time to time in the Annals of Internal Medicine and sponsored by the American Rheumatism Association. Instead, subjects have been chosen that have seemed to us to be worthy of appraisal, and various authors were assigned who were capable of preparing the respective manuscripts. We do not hold necessarily to each and every one of the opinions expressed, in some instances, one or both of us may be rather strongly opposed to some of the printed opinions. This symposium, therefore, is a presentation of individual views, not the summation of the beliefs of the undersigned.

J. H. TALBOTT, M.D.
L. M. LOCKIE, M.D.

Fibrin-like Substances in Collagen-Vascular Diseases

by David S. Howell

ONE OF THE UNSOLVED MYSTERIES in the pathology of collagen-vascular diseases is the origin of fibrin-like substances in several characteristic lesions. During the last decade, medical investigators have detected noteworthy differences in the composition of these materials and have developed new techniques for their study. Despite the publication of lucid reports,[35, 36, 51] misconceptions persist among those not familiar with the subject, viz., that fibrin-like substances are the trademark of collagen-vascular diseases, that their appearance is uniform and that they result primarily from hypersensitivity reactions. The purpose of this study is to clarify these impressions and to discuss important clinical aspects of related research.

HISTORY

As employed here, fibrinoid or fibrin-like substances* (henceforth termed FLS) refer to microscopic granular or fibrillar matter that is eosinophilic, acellular and refractile, revealing some of the tinctoral characteristics of fibrin found with few exceptions in areas of tissue injury. The use of this term precludes any attempt to distinguish between the FLS within blood vessel walls and that within extravascular connective tissue, or between the FLS intimately associated with collagenous fibers and that lying freely in tissue spaces. In addition to the so-called collagen-vascular diseases (rheumatic fever, rheumatoid arthritis, systemic lupus erythematosus, polyarteritis nodosa, scleroderma and, possibly, dermatomyositis), FLS have been described in association with peptic ulcers, Buerger's disease, acute appendicitis, arteriosclerosis, kidney lesions of diabetes mellitus, exudative pneumonitis, tuberculosis, granuloma annulare, subacute bacterial endocarditis, the trophoblastic layer of placental tissues and a variety of experimental tissue responses.[1, 5, 39, 45, 52] Inclusion of these assorted entities is based on a broad definition of FLS without any implications of chemical identification.

In 1880 Neumann first used the word fibrinoid, finding the materials in the surface of inflamed membranes.[49] Since that time, such descriptive phrases as fibrinoid degeneration, fibrinoid swelling, fibrinoid necrosis and fibrinoid change have arisen to describe associated pathologic processes, e.g., those

*Phrase used in reference no. 41

which occur in the evolution of rheumatoid subcutaneous nodules. It was not until 1933 that Klinge suggested common features in the pathogenesis of rheumatic fever, rheumatoid arthritis, polyarteritis nodosa and dermatomyositis based on the presence of similar pathologic changes—the most conspicuous being fibrinoid degeneration.[39] In 1938, Masugi and Ya-Shu added scleroderma,[44] and in 1942 Klemperer, Pollack and Baehr included systemic lupus erythematosus.[37] The designation diffuse collagen disease was devised to refer to the similar morbid alterations of connective tissue in this group. In the same patient, these diseases either seemed to undergo transition from one to the other or else were demonstrated to coexist. Rich in 1946 summarized his observations supporting the possibility of their similar pathogenesis.[52] He studied the disseminated vascular and connective tissue lesions in man resulting from hypersensitivity to sulfonamides, iodides and foreign proteins, and compared them with pathologic changes in anaphylactically sensitized animals. Striking differences in the FLS of systemic lupus erythematosus were reported by Klemperer,[37] and in 1950 he cautioned against the assumption that all these diseases had a common pathogenesis.[34] Many of the studies since that time have been directed toward evaluation of hypersensitivity mechanisms and identification of substances in the fibrinoid lesions.

CLINICAL ASPECTS OF FLS

Although attempts have been made to subclassify FLS on the basis of histologic and histochemical differences, their interpretation often is troublesome because of uncontrollable factors which influence staining reactions. Fibrin, available in highly purified form, has been studied extensively in this regard. Methods of fixation,[64] alterations of ionic strength in the buffer used, pH, length of staining, dye concentration,[55] urea-solubility of the fibrin and presence or absence of critical amounts of albumin or glutathione[17] have been shown to affect profoundly the uptake of dyes by fibrin. Despite the limitations of available methods, considerable information has been accrued through morphologic studies.

Rheumatic Fever. The principal locations of FLS are in the subcutaneous nodules (fig. 1), heart valve lesions, Aschoff bodies, areas adjacent to fibrinous pericarditis, synovial membranes (fig. 2) and rheumatic pneumonitis. FLS first appear in rheumatic fever nodules as an increased volume of material between the fibrillar structures, often in a region of focal vasculitis. Fibroblasts and other cells migrating into the vicinity assemble in a palisade manner and connective tissue fibers regenerate. FLS may develop either intimately associated with collagenous fibers or separate from them, and gradually become swollen, refractile, eosinophilic and granular. In a later stage only amorphous granular debris remains in the central zone which has become necrotic.[3] This process may continue in some lesions to liquefaction and

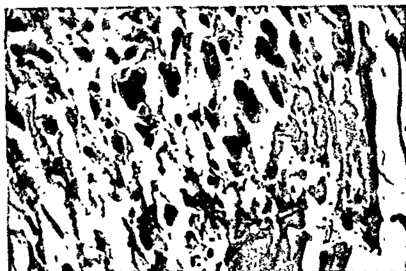


FIG 1 Swollen irregular fibrinoid material between cells in a subcutaneous nodule of rheumatic fever (Courtesy of Arthritis and Rheumatism Foundation)



FIG 2 Fibrinoid change' in synovial membrane of acute rheumatic fever There is intimate association of fibrin like substances with swollen and acidophilic collagenous fibers Interspersed between fibroblasts is an infiltration of mononuclear cells (Courtesy of Arthritis and Rheumatism Foundation)



FIG 3 Synovial membrane of rheumatoid arthritis Palisaded cells and extrusion of masses of fibrinoid substances from beneath the synovial surface forming "rice bodies" (Courtesy of Dr L. Sokoloff)



FIG. 4 Rheumatoid subcutaneous nodule demonstrating central region of fibrinoid necrosis surrounded by palisaded cells and a rim of young connective tissue fibers (Courtesy of Arthritis and Rheumatism Foundation)

in others to cicatrization. Fibroblasts can migrate on the bridgework thus formed by FLS and young collagenous fibers can be supported by it. Whereas in subcutaneous nodules the new fibrillar material takes the typical blue stain of fibrin with phosphotungstic acid hematoxylin, this color rarely develops in the FLS of Aschoff bodies.

Rheumatoid Arthritis. Subcutaneous nodules of rheumatoid arthritis resemble those of rheumatic fever In addition to appearing beside the fibrinous exudates on the synovial membrane, FLS may generate well below the synovial surface (fig. 3). Here, particularly early in disease, fibroblasts form palisades, as in peripheral nodules (figs 4 and 5).[9, 41] Sokoloff has evidence that some masses of FLS may be extruded on the synovial surface as "rice bodies" (fig. 3)[56] FLS are seen in cartilage beneath an eroding pannus, in pleura, pericardium, myocardium, heart valves and the connective tissue supporting skeletal muscle, and vasuclar walls.

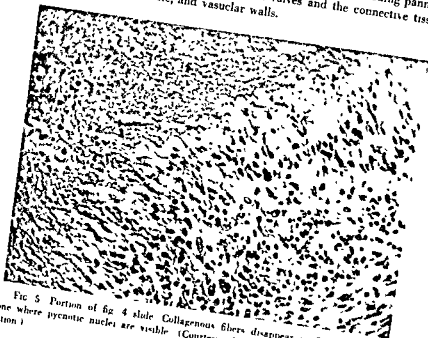


Fig 5 Portion of fig 4 slide Collagenous fibers disappear in fibrinoid necrotic zone where pycnotic nuclei are visible (Courtesy of Arthritis and Rheumatism Foundation)

Systemic Lupus Erythematosus Fibrinoid material deposits between the basement membrane and Bowman's capsule in the kidney The glomerular tufts often contain intensely eosinophilic and thickened glomerular capillary walls—wire loop lesions (fig. 6) Hyaline thrombi occur in parts of many or

in a few glomeruli (fig. 7). The characteristic halo surrounding these plugs is uncommonly manifested by other collagen-vascular diseases[8] Eosinophilic change and baso-eosinophilic smudges or intensely basophilic (hematoxylin) bodies are scattered throughout the heart wall and are observed in the verrucous lesions of Libman-Sachs endocarditis. Basophilic deposits may be in the synovial membrane (fig. 8) and in skin also. These materials stain positively with Feulgen's reagent and show ultraviolet light absorption in the range of desoxyribonucleic acid.[34, 36] Small amorphous clumps identified in blood smears have the same staining properties and comprise the central inclusion bodies of L.E. cells. Further studies on the histochemical nature of these clumps suggest that in their formation from nuclear matter, histone has been removed, and the depolymerization of desoxyribonucleic acid is questioned[21]

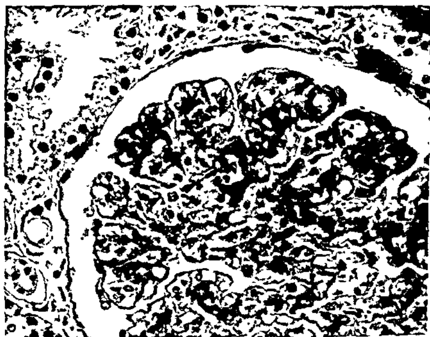


FIG. 6 *Another example of fibrinoid substances in the kidneys of systemic* lupus erythematosus Thickened baso-eosinophilic walls of the glomerular capillaries comprise so-called wire-loop lesions Hyaline thrombi and wire-loop lesions often occur independently (Courtesy of Bunim, J J et al Circulation *14*: 125, 1956)

Scleroderma. The most frequent site of involvement is the glomerular capillaries of the kidneys. In the capillary walls, the thickened eosinophilic regions differ in texture from that of wire-loop vessels of lupus kidneys

Often there is difficulty demonstrating FLS in the lesions of patients with widespread progressive systemic sclerosis. The appearance of the lesions in scleroderma kidneys resembles closely that of necrotizing arteriolitis of malignant hypertension. Inasmuch as the small arteries of the kidneys in scleroderma reveal fibrinoid changes and sclerosis, it is likely that similar arterial changes occur in the afflicted extremities partially explaining the development of Raynaud's phenomenon [57]

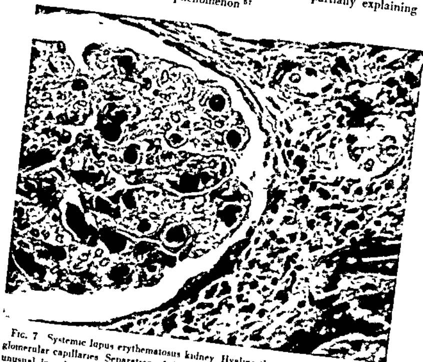


Fig. 7 Systemic lupus erythematosus kidney Hyaline thrombi are within the lumen of glomerular capillaries Separation of the thrombi from the walls by a space (or halo) is unusual in other collagen vascular diseases. (Courtesy of Bunim J J et al. Circulation 14 125, 1956)

Polyarteritis Nodosa Cloudy swelling and necrosis of the media of middle and small sized arteries and veins take place early, together with infiltration of polymorphonuclear leucocytes. Later these are replaced by lymphocytes, monocytes and plasma cells. Thrombosis or aneurisms may develop if the vessel wall is severely damaged The preponderance of pathologic lesions demonstrates ample evidence of FLS in one or all of the arterial coats and surrounding connective tissue Lesions are widely scattered and segmental Panarteritis is illustrated in experimental lesions (fig 13)

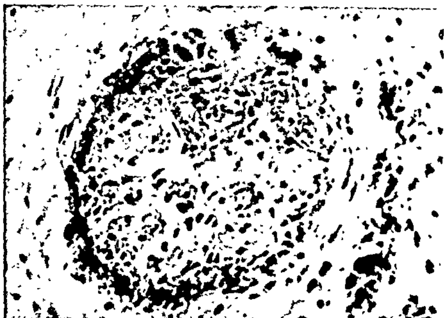


FIG 8 Synovitis of systemic lupus erythematosus showing small inflamed blood vessels Irregular basophilic granules (hematoxylin bodies) are scattered throughout the surrounding tissue (Courtesy of Arthritis and Rheumatism Foundation)

TISSUE ORIGIN OF FLS

It is likely that in the above named diseases the majority of symptoms and signs and ultimate clinical course can be ascribed to the location and severity of tissue injury The frequent appearance of FLS in a damaged region continues to stimulate interest in their origin. Many studies on FLS have been planned with the assumption that one or two major factors are instrumental in their production. Analysis is rendered more complex by the local deposition of nonspecific products of cellular autolysis and inflammation. Likely sources of FLS—according to present concepts—are evaluated below

Collagenous Fibers The chemical fate of collagenous fibers in FLS has been approached by comparing fibers from pathologic and normal tissues The principal ingredient of collagenous fibers is protein collagen. Surprising uniformity of collagen's hydroxyproline content (12 per cent in mammals) and its limitation primarily to collagen and elastin in connective tissue offer investigators a tool for study. A high hydroxyproline content in FLS might be expected if degraded collagen composes the bulk of these substances However, when this index of collagen was applied to trypsin or alkali extracts of rheumatoid nodules, a disappointingly small amount of the amino acid

was found, and clostridial collagenase failed to digest the extracted fibrinoid material.[4,69] Furthermore, when collagen was separated from nodules and synovial membrane of patients with rheumatoid arthritis, the total hydroxyproline within the nodule could be accounted for in collagen and elastin fractions, indicating that little or none was in the extracted FLS.[31] Results support the hypothesis that either the fibrils of collagen were left intact or that decomposition resulted in rapid removal of the hydroxyproline. It would

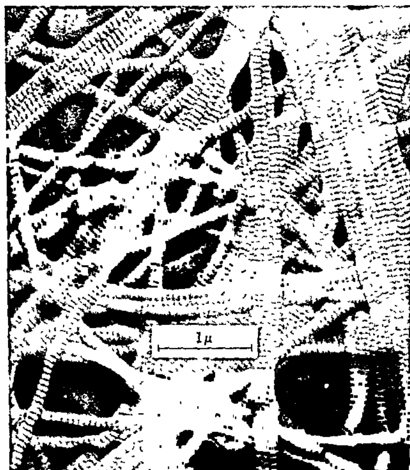


FIG. 9. Electron micrograph of bundles of normal collagen fibrils teased from human corium revealing characteristic periodicity 29000x. Fibrils obtained from subcutaneous nodules of rheumatic fever and rheumatoid arthritis have been indistinguishable from these. (Courtesy of Dr. J. Gross.)

be of interest to analyze the fibrinoid extracts for glycine and proline, which also form a constant proportion of the collagen molecule.

Another approach is the comparison of the physical characteristics of collagen from normal tissues with that from collagen-vascular disease. It is now known that even the smallest normal collagenous fibers visible through the familiar light microscope reveal remarkable periodic cross-striations by electron microscopy (fig 9). Six or more crossbands have been described in each segment, and with some variation the length of each segment averages 640 angstrom units.[25] Collagen fibrils obtained from an assortment of tissues in mammalian species show these structural features. The 640 angstrom spacing agrees with Baer's x-ray diffraction studies of collagen composition.[2] Abnormally formed collagen may lack this periodicity.[30] Kellgren et al, examined the fibrinoid area of rheumatoid nodules by electron microscopy and x-ray diffraction. No remnants of collagen were detectable (fig. 10). The x-ray powder diagrams were those of an amorphous protein.[33] When material from lesions of rheumatoid arthritis, rheumatic fever, systemic lupus erythematosus and scleroderma were studied by electron microscopy in other labora-

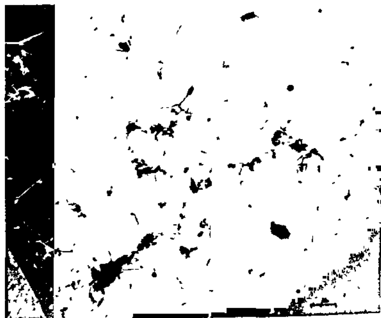


FIG 10 Electron micrograph of fibrinoid substances from a rheumatoid subcutaneous nodule No structures resembling collagen fibrils are visible The x ray diffraction pattern of this material was that of neither collagen nor fibrinogen but suggested an amorphous protein (Courtesy of Kellgren, J H et al: Nature, London *168* 493, 1951)

tories, no evidence of abnormal collagen fibrils could be seen.[16, 24] However, Wolpers reports encountering a few swollen fibrils without cross-striations in electron micrographs of necrotic areas in old rheumatoid nodules. He observed none in fibrinoid regions without necrosis.[66]

Contrary evidence that degenerating collagen contributes to FLS in collagen-vascular diseases rests largely on morphologic studies utilizing enzymatic as well as silver impregnation techniques. Components of FLS were removed or altered by digestion with clostridial collagenase in rheumatic fever nodules.[20] Von Albertini found that silver impregnation of collagen fibers develops concurrently with swelling and fibrillation in rheumatoid and rheumatic lesions. He concluded that fibrinoid degeneration is the preliminary phase of necrobiosis of collagen. In contrast, the FLS he noted in bursitis, chronic fibrinous pneumonia, placental fibrinoid and experimental allergic tissue reactions did not retain silver, and were considered to represent different pathologic processes typified by an infiltration of exuded fibrin.[62, 63] Inasmuch as initial collagenous fiber swelling and fibrillation in part represent decomposition of components cementing the fibrils, the effect of these substances upon silver impregnation needs further clarification. Discrepancies recorded in some reports on FLS susceptibility to enzymes are not yet resolved, but lack of uniformity in methods and criteria for identification of FLS are partially responsible.[14, 20, 43, 60] Nevertheless, the weight of current evidence suggests that the amount of degenerated collagen existing in FLS of rheumatic or rheumatoid nodules is insignificant unless the collagen has been altered in the process of destruction to such an extent that important perimeters of its presence are lost or changed. Kellgren believes that peptides from degraded collagen might produce tissue inflammatory changes with little participation in FLS formation.[32]

Ground Substance. Components of ground substance probably are essential to production of FLS.[14] Ground substance refers to the complicated gel-sol system of proteins, carbohydrates and lipids plus the electrolytes, water and plasma proteins occupying the space between the fibers and cells outside the blood and lymph vessels. Mucopolysaccharides isolated from the mesenchymal tissues occur as salts rather than free acids. Of particular import are hyaluronic acid and the chondroitin sulphates A, B and C. These compounds have a high molecular weight and each repeating unit consists of a disaccharide composed of hexuronic acid and a hexosamine in equimolar proportions.[47] These mucopolysaccharides in combination with proteins probably contribute to the gel like structure of the ground substance and are believed to behave as linear polyelectrolytes capable of binding water and diffusible ions.[44] Hyaluronic acid is found chiefly in synovial fluid, vitreous humor and umbilical cord but not in cartilage, while the group of chon-

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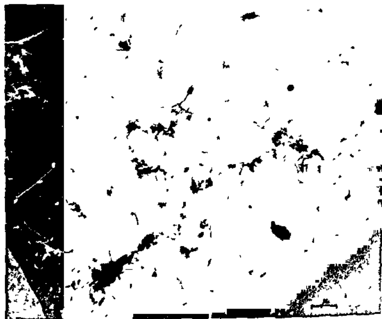


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droitins appears in cartilage, bone, ligaments, tendon, corium, heart valves and aorta. Most of these mucopolysaccharides are hydrolyzed by testicular hyaluronidase.[47] They are believed to exist free and in loose combination with proteins and should be distinguished from glycoproteins and serum mucoids which may infiltrate the ground substance. Thus, the connective tissue areas where FLS are found contain a number of complex carbohydrate compounds with an abundance of acidic groups. Precipitated fibrinoid material conceivably might result through a reaction between available positively charged groups on polysaccharides and those negatively charged on proteins[1] Consistent with this possibility are the findings that in vitro, acid mucopolysaccharides readily form precipitates with extrafibrillary proteins.[1] In experimental tissue injury, fibrinoid degeneration may be accompanied by an increase of free acid mucopolysaccharides and mucoproteins[43] In the quartz granuloma, nonhexosamine-containing polysaccharides appear during the stage of reticulin formation.[30] Consden and co-workers found a significantly larger content of the carbohydrate fraction in nodules from rheumatic fever patients than in normal connective tissue. This extracted material was rich in a galactose-containing polysaccharide.[10] In FLS from a panorama of diseases, increased carbohydrates was suggested histochemically by the presence of metachromasia* and specific removal of this staining reaction by hyaluronidase.[1] However, data are lacking to indicate a reaction between mucopolysaccharides and fibrinogen or other proteins producing FLS

Plasma Proteins FLS tend to accumulate in areas subject to liberal exudation of plasma from capillaries probably rendered more permeable by local injury.[3] Thus, common sites of FLS are alveoli in rheumatic pneumonitis, renal glomerular capillaries, other blood vessel walls and proximate connective tissue. Tyrosine, cystine, cysteine and tryptophane—amino acids present in plasma proteins but absent or low in collagen—have been detected in FLS of collagen-vascular diseases.[48] Any of the plasma proteins are candidates for precipitation in fibrinoid regions In the case of fibrinogen, in vitro studies on coagulation suggest that this precipitation would result through its conversion from the globular to the fibrous state, under the influence of tissue thromboplastic substances.[18] By electron microscopy, fibrinogen molecules appear to be polymerized by action of thrombin to generate crystal-like, needle-shaped protofibrils which then become aligned by lateral association into fibrin strands[51] This reaction is accompanied in vitro by the removal of two polypeptides from the fibrinogen molecule.[58] Through undamaged capillary walls fibrinogen diffuses slowly because of its large molecular size (M W 450,000) and has been identified in normal interstitial tissues[17] FLS

*For example, purple-red coloration with toluidine blue stain used by pathologists detects the presence of tissue acid mucopolysaccharides and other charged polyelectrolytes

occurrence in cartilage and deep in heart valve scar tissue might require that fibrinogen reach these areas by diffusion over a considerable distance.

One of the most intriguing developments in analytical pathology is the use of antibodies labeled by diazotization with fluorescein isocyanate.[11] In this method, tissue sections are overlaid with a solution of labeled antibody which becomes attached specifically to the antigen wherever it exists. After the excess antibody solution is washed away, the antigen site is identified by bright yellow-green fluorescence under ultraviolet light. Rabbits were immunized to purified human fibrin and fluorescein was attached to the resultant rabbit antifibrin globulin. When tissues from patients with rheuma-

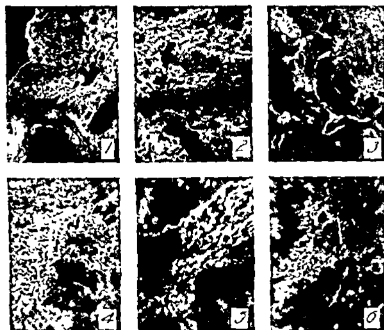


FIG. 11. Photomicrographs of tissue sections stained with fluorescein-labeled rabbit anti-human fibrin. Specific fluorescence due to fixation of labeled antibodies with antigen in the sections is shown by the white areas. *Slide 1*. Fibrin on the serosal surface of an inflamed appendix. 100x. *Slide 2*. Fibrinoid staining for fibrin in the submucosa of same appendix. 210x. *Slide 3*. Section of normal human placenta. Collagen fibers and fibrin strands are intermingled, as shown by arrows. 100x. *Slides 4, 5, 6*. Rheumatoid subcutaneous nodules. Areas of fibrin-like substances are composed of fibrin strands and masses. In Slide 6, round gray masses are older dense bundles of collagen among swollen reticular fibers in the necrotic center. 210x. (Courtesy of Dr. D. Gitlin, et al., Am. J. Path. 33: 55, 1957.)

toid arthritis (fig. 11), rheumatic fever, glomerulonephritis and polyarteritis nodosa were exposed to this tagged antifibrin antibody, an intense fluorescence was found in the fibrinoid vicinities. Fluorescent antifibrin was noted in the wire-loop lesions of a patient with systemic lupus erythematosus and about the inflammatory cells of necrotic muscle in another patient with dermatomyositis. In addition, this fluorescent antibody was fixed in the FLS of normal placentas (fig 11), uremic pneumonitis and the hyaline thrombi of thrombotic thrombocytopenic purpura [12, 13] Some studies have revealed *no consistent differences histochemically* between purified fibrin and FLS from rheumatic lesions [41, 48] These investigations confirm the view that FLS contains fibrin or fibrinogen in a spectrum of collagen-vascular lesions

The fluorescent antibody technique has been applied to the study of gamma globulin in connective tissue of patients with collagen-vascular and other diseases. Such studies are of special interest because of the historical search for anaphylactic hypersensitivity reactions between tissue-fixed antigens and circulating antibodies In experimental nephritis, localization of specific fluorescent antikidney serum in the basement membranes of glomeruli was shown.[27] However, antigens which would fix antibodies to tissues have not been isolated in the collagen-vascular diseases and efforts are limited to localization of gamma globulins, as yet without immunologic specificity. Tagged rabbit antihuman gamma globulin was localized in the arterial lesions



FIG 12 Photomicrograph of rheumatoid nodule stained intensely with fluorescein labeled rabbit anti human gamma globulin (Courtesy of Dr Frank J Dixon) There is a lack of fluorescence at the periphery corresponding to the region of palisading cells and surrounding connective tissue 48x

of polyarteritis nodosa and in the glomeruli of acute and chronic glomerular nephritis.[45] The kidney of a patient with systemic lupus erythematosus showed in the glomeruli and arterioles a relative abundance of gamma globulin and little albumin in areas of fibrinoid change.[45] Similar findings were noted in the subcutaneous nodules of patients with rheumatoid arthritis (fig 12) and in the altered heart valves, as well as the myocardial connective tissue of patients with rheumatic heart disease More albumin and less gamma globulin were found in the exudate of acute appendicitis.[61] However, in a patient with a diagnosis of rheumatoid arthritis and agammaglobulinemia studied by Gitlin,[18] no gamma globulin was detected in biopsies of synovium, skin or muscle.

Cells Fibroblasts are believed to produce mucopolysaccharides and precursors of collagen,[14] so that these cells may contribute indirectly to FLS. It seems likely that local release of polypeptides, enzymes, nucleoproteins and other factors from inflammatory cells might be critical in the induction of FLS.[47, 48] An enzyme has been isolated from leukocytes and synovial tissue which alters a mucoprotein of cartilage.[67] In the synovial fluid of acutely diseased joints, important enzymes are liberated, apparently as a consequence of the local inflammation [28, 68] Fibrinoid substances in angiitis usually are adjacent to lining cells, so that the likelihood of direct accumulation of cellular ingredients in FLS seems greater. In necrotizing arteritis, hyaline necrosis of the vascular smooth muscle develops This smooth muscle is believed by some authors to be a source of experimental fibrinoid substances.[9] It is suggested that intravascular lesions of polyarteritis nodosa result from severe spasm of smooth muscle secondary to hypersensitivity reactions (Schultz-Dale effect).[62] Altered nuclear material from leukocytes and possibly other cells is found in the FLS of systemic lupus erythematosus and forms the hematoxylin bodies [36]

FLS IN EXPERIMENTAL TISSUE RESPONSES

Animal syndromes resembling human collagen-vascular diseases have been sought extensively. This problem frequently is approached through immunologic techniques. The Arthus reaction, parallel in many respects to anaphylaxis, is a localized necrotizing inflammatory response attending an antigen antibody union It has been provoked in the skin, joints, eye, kidney, liver, lung, brain and isolated blood vessels[35] Fibrinoid substances appear in the affected tissues,[44] and alterations in collagen fibrils are found [33] Purified protein fractions were administered to rabbits by Hawn and Janeway. Injection of bovine albumin resulted most often in periarteritis like lesions but renal changes followed globulin injection [26] In the inflammation of *delayed* hypersensitivity (of which the prototype is the tuberculin reaction), fibrinoid material may exist [3] Here, antibodies are fixed to the cells of the host rather

than found in circulation, as in anaphylaxis. A third type of immunologic phenomenon employed in exploring the pathogenesis of collagen-vascular diseases is the auto-antibody system, which involves the use of antibody and antigen derived from the same species. Efforts have been made to produce fibrinoid lesions by utilizing as antigen killed streptococci mixed with rat kidney or heart. In other experiments, streptococci or staphylococci in conjunction with tissue extracts were employed. Inconstant results have been obtained by these methods.[15] Purified fractions of human connective tissues failed to demonstrate antigenicity.[13]

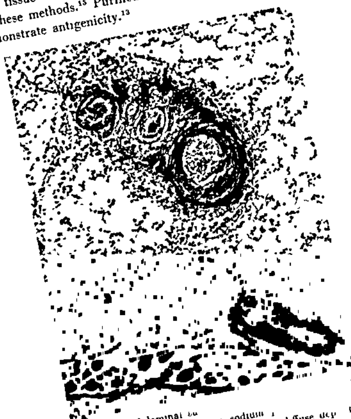


Fig. 13 Section from abdominal [illegible] rificed 24 hours after subcutaneous injection of 1 milligram sodium [illegible] intravenous administration of 250 micrograms of E. coli endotoxin. A diffuse dep[illegible]tion of fibrin like substances in the vessel walls is associated with a cellular reaction resembling that of polyarteritis nodosa. (Courtesy of Brunson, J. G. et al.) 165x.

In addition to local and systemic anaphylactic hypersensitivity reactions,[26, 28, 48] FLS are described in experimental wounds,[3] vascular lesions of frostbite,[40] experimental arthritis,[5] croton oil lesions[43] and in the vasculature of animals treated with large amounts of desoxycorticosterone.[54] Intra-

venous injection of a high dosage of adrenalin in dogs produced general vascular damage, including fibrinoid necrosis of arterial media and pan arteritis with periarterial exudate in the gut, heart and other organs.[55] Damage was blocked by previously administered intravenous dibenamine Fibrinoid deposits probably resulted from vascular injury secondary to the production of intense vasoconstriction, ischemia and hypertension Similar lesions were induced by massive blood transfusions or infusion of renal extracts. Experimental hypertension originating through other methods may cause fibrinoid alteration in arterial walls.[52] Rapid appearance of necrotizing fibrinoid arteriolitis in patients with scleroderma kidneys might follow a progressive ischemia attending the fibrotic constriction of the intralobular arteries.[57] In rabbits, disseminated lesions resembling those of patients dying of acute collagen-vascular disease were produced when small amounts of E. coli endotoxin and an acidic polymer, sodium polyanethol sulfonate



Fig. 11 Renal glomerulus from a rabbit given E. coli endotoxin by two in
venous injections 18 hours apart Animal died within 12 hours after second inject
Glomerular capillaries are filled by masses of homogeneous hyaline fibrinoid mate
Hematoxylin and eosin stain (Courtesy of Brunson J G et al) 450x

(Liquoid), were given intravenously.[7] Liquoid injected into the skin of rabbits produced little effect, but when it was accompanied by an intravenous injection of E. coli endotoxin, there appeared lesions similar to polyarteritis nodosa with deposits of fibrinoid material in and about the walls of the medium-sized and small arteries (fig. 13). When the Shwartzman reaction induced by two spaced injections of E. coli endotoxin was used (fig. 14), protection was effected by nitrogen mustard. Based on considerable data, the authors feel that a consistent ingredient of FLS in these experiments was altered fibrinogen.[23, 59, 60]

CONCLUSION

Fibrin-like substances (FLS) are difficult to define because of variations in appearance and behavior related to the disease, stage of a single lesion, anatomy of the tissue site and differences in methods of detection. Apparently, fractions of the ground substance in connective tissue are prominent contributors to FLS formation, but participation of collagen degeneration per se remains unsettled. Disseminated fibrinoid lesions are induced by multiple techniques involving, it seems, the one common denominator of tissue injury. Some recent studies favor a pathogenic role for anaphylactic hypersensitivity in the collagen-vascular diseases, but morphologic similarities—including the FLS—while consistent with these concepts do not provide specific positive evidence. The terms collagen, diffuse collagen or collagen-vascular disease offer an adequate temporary scaffolding to be used until the fundamental nature of their origin is known Aided by newer physicochemical and histopathologic methods, continued progress in separating the identities within the collagen-vascular disease group may be expected.

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References

1 Altshuler, C H, and Angevine, D M Histochemical studies on the pathogenesis of fibrinoid Am J Path: 25 1061, 1949
2 Bear, R S Long x-ray diffraction spacings of collagen. J Am Chem. Soc 64 727, 1942
3 Bennett, G A Pathology of connective tissue, fibrinoid degeneration In Tr Conf Connective Tissues Josiah Macy, Jr 1 44, 1950
4 Bien, E J and Ziff, M Fibrinoid and hydroxyproline of the rheumatoid subcutaneous nodule Proc Soc Exper. Biol & Med 78 327, 1951

5. Bocking, D and Brien, F S Comparative pathology of experimental arthritis due to formalin, blood, immediate and delayed type hypersensitivity reactions. Ann Rheumat. Dis. *14* 99, 1955

6 Booth, E., Muirhead, E. E. and Montgomery, P O'B The "fibrinoid of renal cortical necrosis due to the Schwartzman reaction Arch Path *61* 169 1956.

7 Brunson, J G., and Davis, R L Systemic fibrinoid diseases Arch Path. *60* 593, 1955

8 Bunim, J J., Harvey, A M., Bollet, A J., Hilbish, T F, Van Scott E, Sokoloff L., and Brecher, G.. Systemic lupus erythematosus, clinical conference Circulation 14 125, 1956

9 Bunim, J J., Sokoloff, L., Williams, R R and Black, R L Rheumatoid arthritis a review of recent advances in our knowledge concerning pathology diagnosis and treatment J *Chron.* Dis 1 168, 1955

10 Consden, R., Glynn, L. E. and Stanier, W M A chemical examination of connective tissue in rheumatic fever. Biochem J 55 248, 1953

11 Coons, A H Histochemistry with labeled antibody Bull New York Acad Med 32 168, 1956

12 Craig, J M and Gitlin, D. The nature of the *hyaline* thrombi in thrombotic thrombocytopenic purpura Am J Path, Jan, 1957 (in press)

13 Dresner, E. Aetiology and pathogenesis of rheumatoid arthritis Am J Med *18* 74, 1955

14 Fawns, H T and Landells, J W Histochemical studies of rheumatic conditions II The nodule of rheumatoid arthritis Ann Rheumat Dis *13* 28, 1954

15 Fischel, E The role of allergy in the pathogenesis of rheumatic fever Am J Med 7. 772, 1949

16 Gale, J C. Electron microscope studies of collagen from normal and diseased tissues Am J Path 27 455, 1951

17 Gitlin, D, and Craig, J M Variations in the staining characteristics of human fibrin. Am J Path. 33 267, 1957

18 Gitlin, D., Craig, J M., and Janeway, C A Studies on the nature of fibrinoid in the collagen diseases Am J Path 33 55 1957

19 Gitlin, D, Landing, B H and Whipple, A The localization of homologous plasma proteins in the tissues of young human *beings* as demonstrated with fluorescent antibodies. J Exper Med 97 163, 1953

20 Glynn, L. E. and Loewi, G Fibrinoid necrosis in rheumatic fever J Path & Bact 64 329, 1952.

21 Godman, G C, Deitch, A D and Klemperer, P On the composition of the hematoxylin bodies of systemic *lupus* erythematosus Am J Path *32* 616, 1955

22 Goldblatt, H Studies on experimental hypertension VII The production of the malignant phase of hypertension J Exper Med *67* 809, 1938

Good, R., and Thomas, L Studies on the generalized Schwartzman reaction IV Prevention of the local and generalized Schwartzman reactions with heparin J Exper Med 97 871, 1953

Gross, J., Schmitt, F O., and Highberger J H *In vitro* fibrogenesis of collagen In Tr Conf Metabolic Interrelations Josiah Macy, Jr Foundation 4 32, 1952

25 Gustavson, K H The Chemistry and Reactivity of Collagen New York, Academic Press, 1956

26 Hawn, C. Z. and Janeway C. A Histological and serological sequences in experimental hypersensitivity J Exper Med 85 571 1947

27 Hill, A G S and Cruickshank, D. A study of antigenic components of kidney tissue Brit J Exper Path. 34 27, 1953

28 Humphrey, J H and Pagel, W.: Tissue response to heat-killed streptococci in the skin of normal subjects, and in persons with rheumatic fever, rheumatoid arthritis, subacute bacterial endocarditis and erythema nodosum Brit. J Exper Path 30. 282, 1949

29 Jacox, R F, and Feldman, A Variations of beta glucuronidase concentration in abnormal human synovial fluid J Clin Investigation 34 261, 1955

30 Kantor, T G and Schubert, M The relation of mucoprotein, mucopolysaccharides and collagen formation Ann Rheumat Dis 14 95, 1955

31 Kantor, T, Sokoloff, L, Smith, A, and Ziff, M: Chemical and histological studie of the fibrinoid material of the subcutaneous rheumatoid nodule. Ann Rheumat Dis 10 471, 1951

32 Kellgren, J H Some concepts of rheumatic disease Brit M. J 1 1093, 1152, 1952

33 Kellgren, J H, Ball, J, Astbury, W T., Reed, R., and Beighton, E: Biophysical studies of rheumatoid connective tissue Nature 168: 493, 1951

• 34 Klemperer, P: Concept of collagen diseases Am J Path 26 505, 1950

35 Klemperer, P The pathogenesis of lupus erythematosus and allied conditions Ann Int Med 28 1, 1948

36 Klemperer, P The significance of the intermediate substances of the connective tissue in human disease Harvey Lectures 49 100, 1953-54

37 Klemperer, P, Pollack, A D and Baehr, G: Diffuse collagen disease, acute disseminated lupus erythematosus and diffuse scleroderma J A M A 119. 331, 1942

38 Klinge, F Der Rheumatismus Ergebn Allg Path u Path Anat 27. 1, 1933

39 Koss, L G Hyaline material with staining reaction of fibrinoid in the renal lesions of diabetes mellitus Arch Path 54 528, 1952.

40 Kulka, J P, and Blair, J R The vascular and articular lesions of frostbite Rheum Dis 15 65, 1956

41 Kulka, J P, Bocking, D, Ropes, M W and Bauer, W Early joint lesions rheumatoid arthritis, report of eight cases with knee biopsies of lesions of l than one year's duration Arch Path 59 129, 1955

42 Lewis, T: Blood Vessels of the Human Skin and their Responses London, Sha & Sons, 1927

43 Luft, A-M P A and Pearce, R H The chemical changes in connective tissue resulting from injury Ann Rheumat Dis 15 65, 1956

44 Masugi, M and Ya-Shu Die diffuse Sklerodermie und ihre Gefassveranderung Virchows Arch f path Anat 302 39, 1938

45 Mellors, R C and Ortega, L G Analytical pathology; new observations on the pathogenesis of glomerulonephritis, lipid nephrosis, periarteritis nodosa and secondary amyloidosis in man Am J Path 32 455, 1956

46 Menkin, V Biochemistry of inflammation Lancet 1. 660, 1947

47 Meyer, K Chemistry of connective tissue polysaccharides. In Tr Conf Connective Tissues. Josiah Macy, Jr Foundation 1 88, 1950

48 Movat, H Z and More, R H The nature and origin of fibrinoid Am J Path 32 614, 1956

49 Neumann, E Die Picrocarminfarbung und ihre Anwendung auf die Entzündungslehre Arch f mikr Anat 25 130, 1880

50 Porter, K R Repair processes in connective tissue In Tr Conf Connective Tissues Josiah Macy, Jr Foundation 2 126, 1951

1 Porter, K R, Hawn, C Z Sequences in the formation of clots from purified bovine

fibrinogen and thrombin a study with the electron microscope J Exper Med 90 225, 1949
52 Rich, A R: Hypersensitivity in disease with especial reference to periarteritis nodosa, rheumatic fever, disseminated lupus erythematosus and rheumatoid arthritis Harvey Lectures 42 106, 1946 47
53 Rich, A R, Voisin, G A and Bang, F B Electron microscopic studies of the alteration of collagen fibrils in the Arthus phenomenon Bull Johns Hopkins Hosp 92 222, 1953
54 Selye, H General adaptation syndrome and diseases of adaptation J Clin Endocrinol 6 117, 1946
55 Singer, M and Morrison, P R Influence of pH dye and salt concentration on the dye binding of modified and unmodified fibrin J Biol Chem 175 133 1948
56 Sokoloff, L: Experimental and human pathology Program of 2nd Nat'l Conf on Research and Education in Rheumatic Diseases, Bethesda, Md Dec, 1956
57 Sokoloff, L.: Some aspects of the pathology of collagen diseases Bull New York Acad Med 32 760, 1956
58 Symposia of the Soc for Exper Biol, No 9 Fibrous proteins and their biological significance New York, Academic Press, 1955
59 Thomas, L: Mechanisms involved in the vascular lesions produced by endotoxins Bull New York Acad Med 31 861, 1955
60 Thomas, L., Smith, R, and Von Korff R Studies on the generalized Schwartzman reaction VII The role of fibrinogen in the deposition of fibrinoid after combined injections of endotoxin and synthetic acidic polymer J Exper Med 102 263, 1955
61 Vazquez, J J and Dixon, F J Studies on the immunohistochemical composition of inflammatory and degenerative lesions Am J Path 32 615, 1956
62 von Albertini, A: Bedeutung der allergielehre fur die Pathologie Schweiz. Ztschr allg Path. 17 1, 1954
63 von Albertini, A Zum begriff der fibrinoiden Degeneration Schweiz. Ztschr f allg. Path 6 417, 1943
64 Wagner, B M: Histochemical studies of fibrinoid substances and other abnormal tissue proteins 1 Application of Rogue's chromotrope stain Arch Path. 59 58, 1955 2 Effect of fibrinolytic enzymes 59 63, 1955
65 Waters, L. L. and de Suto-Nagy, G. I Circulatory factors in pathogenesis of experimental arteriolar necrosis Yale J Biol & Med 22 751, 1950
66 Wolpers, C Elektronenmikroskopische Untersuchungen zur Pathologie kollagener Fasern Frankfurt Ztschr Path 61 417 1950
67 Ziff, M., Gribetz, H J and Lospalluto, J Effects of leucocytes and rheumatoid synovial membrane on the viscosity of a mucoprotein obtained from cartilage Ann Rheumat. Dis 14 412, 1955
68 Ziff, M., Simpson, J, Scull, E., Smith, A, Shatton J, and Mainland, D Amino tripeptidase content of synovial fluid in arthritic diseases J Clin Investigation 34 27, 1955
69 Ziff, M., Kantor T, Bien, E, and Smith A Studies on the composition of the fibrinoid material of the subcutaneous nodule of rheumatoid arthritis J Clin Investigation 32 1253, 1953

Serologic Reactions in Rheumatoid Arthritis

by Charles Ragan

THE SEROLOGIC REACTIONS that are fairly specifically associated with rheumatoid arthritis will be discussed in this section. These do not include the many nonspecific reactions of inflammation seen in other connective tissue syndromes and inflammatory conditions, such as the erythrocyte sedimentation rate (ESR), C-reactive protein, hyperglobulinemia (elevated α^2 and gamma globulin) and hypoalbuminemia. Usually, with the administration of large amounts of anti-inflammatory steroids, these nonspecific reactions will change toward normal The specific serologic reactions remain essentially unchang under these circumstances[1] and therefore may constitute a fundamental pa of the disease process, in contrast to the nonspecific reactions, which consti tute a host response *to* the disease.

Historically, the streptococcus agglutination (SA) reaction was the first to be described[2] Originally it was thought to indicate a pathogenic role for a particular streptococcus. Subsequently, the reaction was found to take place with most group A hemolytic streptococci and a few pneumococci and staphylococci[3] Wallis[4] implied from his work with Kaolin particles that the streptococci were solely inert carriers Lamont-Havers[5] finally clarified the problem by showing that two serum factors were at work in the reaction, the first a nonspecific, water-soluble one—probably a coccal antibody that presumably coated the streptococci—and the second a disease-specific water-insoluble serum factor that agglutinated the coated streptococci.

The sensitized sheep cell agglutination (SSC) was first described by Waaler[6] in the early forties His work was overlooked until Rose et al.[7] later in the same decade independently described a differential sheep cell agglutination, comparing serum agglutinin titers against normal and sensitized sheep cells A high differential titer was felt to be specific for rheumatoid arthritis In the next several years, a great deal of work was done on this reaction by Heller, who greatly clarified the technical difficulties and immeasurably increased our knowledge of the involved mechanisms Heller pointed out that a differential titer test was not necessary if the normal sheep cell agglutinin was first completely absorbed[8] from the serum to be tested. He then found that sheep serum would augment the agglutination titer in rheumatoid serum more than in control serum[9] This phenomenon has not been generally adopted. Heller[10] noted that pooled human gamm

globulin (Cohn fraction II) interfered with the sensitized sheep cell agglutination. He mixed tanned sheep erythrocytes with pooled human gamma globulin and observed that rheumatoid serum would strongly agglutinate erythrocytes in this system. The advantages of the FII reaction are its standardized components, the ease with which it may be read, and the sensitivity of the system with the serum of patients with rheumatoid arthritis. Because of this last factor, high titers are obtained with agglutinating serums in many instances. The doubtful readings, so frequently observed in the streptococcus and sensitized sheep cell agglutination systems where one or two tubes may make the difference between a positive and a negative reaction, occur much less frequently.

Ziff[11] developed a technique whereby a positively reacting system was inhibited by the euglobulin fraction of normal serum but not by that of patients with rheumatoid arthritis. This he ascribed to the presence of an inhibitor which was itself blocked in the rheumatoid serum by the presence of the rheumatoid factor. Using this technique, he appears to have increased the specificity of the reaction greatly. The technique is difficult and tricky, and to be suitable for routine use it requires careful attention to detail.

Following Heller's observation of agglutination of sheep red cells coated with pooled human gamma globulin, Epstein[12] took the next logical step and was able to demonstrate a precipitin reaction between pooled human gamma globulin and rheumatoid serum. The reaction, like most precipitin reactions, does not have the sensitivity of an agglutination reaction and hence will not at present replace the FII agglutination for routine clinical use. It does, however, provide a definitive tool with which to study the problem with the techniques of immunochemistry.

Very recently, Plotz and Singer[21] have utilized the technique of Latex fixation. They mix standardized particles of Latex with Cohn fraction II and the particles are agglutinated by the serum of patients with rheumatoid arthritis. This is probably the reaction of choice in the clinical laboratory.

The *specificity* of these reactions is dependent primarily upon clinical judgment. The diagnosis of rheumatoid arthritis in its early stages or in atypical disease is difficult, varies from institution to institution and in many instances depends upon the personal whim of the examiner. If the population sampled includes early or atypical instances of the disease, it is possible the percentage of positive reactions will be low. In most such samplings, 50 per cent of patients with rheumatoid arthritis have a positive streptococcus agglutination,[3] 60 per cent have a positive differential sensitized sheep cell agglutination,[11] and 70 per cent a positive FII reaction.[11] Ziff[11] reports over 90 per cent have a positive sheep cell inhibition reaction. If only patients with rheumatoid nodules are tested, over 95 per cent will have a positive reaction

with all four procedures. We have had to search assiduously to find a patient with a histologically proven rheumatoid nodule who had a negative FII reaction. In general, the serum of patients with typical disease is more likely to show a positive reaction, and the incidence of positive reactions increases with longer duration of disease. There are numerous exceptions to this generalization Patients have been observed to have a strongly positive FII reaction 18 hours after the first joint pain; in contrast, we have seen several patients with long-sustained, far-advanced disease with a negative FII reaction. Patients with rheumatoid (Marie-Strumpell) spondylitis, even with the type of peripheral joint involvement identical to rheumatoid arthritis, tend to have serums with fewer positive reactions [11, 13] Patients with psoriasis and rheumatoid arthritis also tend to have sera with fewer positive reactions.[11, 13] Patients with juvenile rheumatoid arthritis, even when the serum is obtained during their adult life, also have fewer positive reactions. Ziff has found that his inhibitor technique will often pick out a positive reaction in this latter group [11] False positive reactions in diseases other than rheumatoid arthritis are relatively infrequent (2 to 5 per cent), with three major exceptions. In rheumatic fever[13]—particularly a prolonged bout—positive reactions may be seen in up to 10 per cent of the patients, in systemic lupus erythematosus, from 25 to 60 per cent,[15] and in diffuse angiitis, quite frequently.[13]

Thus the specificity of the reaction is excellent for that segment of disease known as the "collagen group," with the highest percentage of positive reactions appearing in typical, long-sustained rheumatoid arthritis, especially in the serum of those patients with nodules. In most instances, a serum showing a positive streptococcal agglutination will also show a positive reaction in the other tests. There are, however, rare exceptions The serum factor is probably not identical for the SA and SSC. This may be demonstrated by differential absorption studies.[16] Absorption of serum with FII coated cells will, however, remove all of the factor for SA and SSC,[17, 18] but the converse is not true. Reaction of the FII positive serum with normal gamma globulin will result in precipitate formation and the removal of FII agglutinating activity[12] from the supernatant

The *mechanisms* involved are at present incompletely understood. Current thinking holds that the various particles used—group A streptococci, sheep cells and tanned sheep cells—act as inert carriers for a component of gamma globulin. In the streptococcus agglutination, this is represented by the presumed nonspecific antibody to the streptococci found in the water-soluble fraction. In the sensitized sheep cell agglutination reaction, this is the amboceptor and in the FII reaction, it consists of pooled human gamma globulin. (For unexplained reasons, single gamma globulins isolated by convection or zone electrophoresis are not reactive in the FII reaction but do

react in the precipitin reaction). Several antigen-antibody systems have been shown to react with the rheumatoid factor in a manner similar to the sensitized sheep cell agglutination reaction.[21, 22] Thus, the rheumatoid factor probably represents a material which will combine with some component of human gamma globulin—and with some component of the antiserums formed in response to an apparently heterogeneous group of antigens.

The Rheumatoid Factor This is contained in fraction III (Heller) of serum and is predominantly beta globulin, but contains small amounts of alpha and gamma globulin and a trace of albumin.[18] By paper and convection electrophoresis, the factor lies in or near the gamma globulin.[5, 18] Its relation to complement or a component of complement remains problematical, but crude inactivation of the components of complement has failed to reduce the SSC titer of positive serums.[18]

Partial purification of the factor has shown that the protein nitrogen content of Heller fraction III may be reduced to 70 per cent, the phospholipids to 38 per cent and the total cholesterol to 1 per cent of their original values without loss of titer.[18] All of the agglutinating activity of a euglobulin fraction has been obtained in a fraction containing only 1.6 per cent of the original nitrogen.[20] The activity is lost on heating to 100° C. but is stable in a pH range from 4 to 11 and is impervious to enzymatic treatment with trypsin or papain.[20] Work is now in progress to attempt to characterize the rheumatoid serum factor, the material in pooled human gamma globulin which combines with the factor and the inhibitor.

SUMMARY

The serologic reactions seen in rheumatoid arthritis have a rather good biologic specificity for rheumatoid arthritis, systemic L. E. and diffuse angiitis. Because of its persistence during the administration of large amounts of anti-inflammatory steroids, it may represent an integral part of the disease. The current hypothesis is that the rheumatoid factor reacts with some component of gamma globulin and that there is an inhibitor of this reaction present in all normal human sera. One may anticipate the further purification of these three components—the reactant in pooled gamma globulin, the reactor or rheumatoid factor and the inhibitor. This would constitute a forward step in our understanding of the pathogenesis of this group of diseases.

References

1 Howell, D S and Ragan, C The course of rheumatoid arthritis during four years of induced hyperadrenalism (IHA) Medicine 35 83, 1956.

2 Nicholls, E E and Stainsby, W J. Streptococcal agglutinins in chronic infectious arthritis J Clin Invest 10 323, 1931

3 Dawson, M H, Olmstead, M and Boots, R H Agglutination reactions in rheumatoid arthritis I Agglutination reactions with streptococcus hemolyticus J Immunol 23 187, 1932

4 Wallis, A D Rheumatoid arthritis, introduction to study of its pathogenesis, nonspecific serologic reactions; pneumococcus antibodies. Am J M Sc 212, 716, 718, 1946, Rheumatoid arthritis, agglutination of hemolytic streptococci Am J M Sc 213 94, 1947

5 Lamont Havers, R W Nature of serum factors causing agglutination of sensitized sheep cells and group A hemolytic streptococci Proc. Soc Exper Biol & Med 88· 35, 1955

6 Waaler, E On the occurrence of a factor in human serum activating the specific agglutination of sheep blood corpuscles Acta path et microbiol Scandinav 17 172, 1940

7 Rose, H M, Ragan, C, Pearce, E and Lipman, M O Differential agglutination of normal and sensitized sheep erythrocytes by sera of patients with rheumatoid arthritis Proc Soc Exper Biol & Med 68 1, 1948

8 Heller, G, Jacobson, A S and Kolodny, M H · A modification of the hemagglutination test for rheumatoid arthritis Proc Soc Exper Biol & Med 72 316, 1949

9 Heller, G, Jacobson, A S, Kolodny, M H and Schuman, R L The hemagglutination test for rheumatoid arthritis I An immunological analysis of the factors involved in the reaction J Immunol 69 27, 1952

10 Heller, G, Jacobson, A. S, Kolodny, M H and Kammerer, W H. The hemagglutination test for rheumatoid arthritis II The influence of human plasma fraction II (gamma globulin) on the reaction J Immunol 72· 66, 1954

11 Ziff, M, Brown, P, Lospalluto, J, Badin, J and McEwen, C: Agglutination and inhibition by serum globulin in the sensitized sheep cell agglutination reaction in rheumatoid arthritis Am J Med 20 500, 1956

12 Epstein, W, Johnson, A and Ragan, C Observations on a precipitin reaction between serum of patients with rheumatoid arthritis and a preparation (Cohn Fraction II) of human gamma globulin Proc Soc Exper Biol & Med 91 235, 1956

13 Jacobson, A S, Kammerer, W H, Wolf, J, Epstein, W. V and Heller, G · The hemagglutination test for rheumatoid arthritis III Clinical evaluation of the sheep erythrocyte agglutination (S E A) test and the gamma globulin (FII) tests Am J Med 20 490, 1956

14 Bunim, J J, Sokoloff, L, Williams, R R and Black, R L · Rheumatoid arthritis a review of recent advances in our knowledge concerning pathology, diagnosis and treatment. J Chronic Dis 1 168, 1955

15 Jessar, R A, Lamont-Havers R W and Ragan, C Natural history of lupus erythematosus disseminatus Ann Int Med 38: 717, 1953

16 Lamont Havers, R W Studies on the sensitized sheep cell agglutination reaction of rheumatoid sera Presented in part requirement for the Diploma Course in Medicine, McGill University, Montreal, Canada, 1952

17 Epstein, W and Ragan, C. Unpublished data
18 Heller, G., Kolodny, M. H., Lepow, I. H., Jacobson, A. S., Rivera, M. E. and Marks, G. H. The hemagglutination test for rheumatoid arthritis IV Characterization of the rheumatoid agglutinating factors by analysis of serum fractions prepared by ethanol fractionation J Immunol 74 340, 1955
19 Gerber, D Unpublished data.
20 Lospalluto, J and Ziff, M Purification of the accessory agglutinating factor of the serum in rheumatoid arthritis Proc. Am Rheumatism Assoc meeting, Chicago, June, 1956
21 Vaughan, J H Behavior of the agglutination activating factor of rheumatoid arthritis with immune precipitates. Ann Rheum Dis 14 431, 1955
22 Foz, A., Batalla, E. and Espacio, L. Auto antibodies in rheumatoid arthritis A simple method of demonstration with possible diagnostic application Ann Rheum Dis 14 313, 1955
23 Singer, J M and Plotz, C.M Am J Med. 21: 888, 1956

Arthritides of Domesticated Livestock

by George M. Neher

THE ARCHITECTURE OF THE JOINT has long been recognized as one of nature's masterpieces of design, and the free and painless movement of its lubricated articulations are included in the essential signs of good health. It is perhaps correct to say that all animals are subject to arthritis, whether it be slight self-limiting inflammation stemming from a general systemic disturbance that subsides with the animal's return to health or joint disease which may progress to frank bony alterations and the eventual loss of function. This study is presented with the intention of acquainting the reader in a general way with some of the more important joint disease entities of domesticated livestock (sheep, cattle and particularly swine) rather than of providing a complete survey of the arthritides of animals.

Many of the arthritides of domesticated livestock are somewhat analogous to the various differentiated arthritides of the rheumatic disease group. Probably the best known of these, and certainly the one of greatest economic importance, is the rheumatoid-like arthritis of swine, which bears many parallelisms to the comparable disease of man. In advanced cases where swine are permitted to remain essentially immobile, extensive osteophyte formations and lipping may occur, so that the pathology would appear to suggest osteoarthritis secondary to rheumatoid arthritis. By virtue of its importance to the swine industry and the resemblance it bears to arthritis in man, this disease will receive the bulk of consideration in the following discussion.

In a consideration of degenerative joint disease in farm animals it should be pointed out that geriatric problems in livestock are infrequent, since animals produced for meat purposes (sheep, hogs and beef cattle) are usually slaughtered at a young age, and animals raised for breeding purposes generally are slaughtered when breeding efficiency wanes. Dairy cows are usually kept only as long as they prove to be profitable producers of milk and butterfat. With the widespread practice of artificial insemination, particularly in the dairy industry, and the establishments of bull studs where animals are kept for the commercial production of semen, a degenerative arthritis in aged bulls appears to be an important problem.

The incidence of osteoarthritis appears to be greatest in the Holstein-Friesian breed and may exceed 20 per cent in bulls over nine years old, according to Bartlett.[1] The onset of the disease in some cases may be in-

sidious; in many instances, however, it appears to be associated with trauma to a specific joint and later has a tendency to become polyarthritic in nature. Remissions and exacerbations are characteristics of the early disease. In some instances hydrocortisone therapy (intra-articular) is beneficial. The housing of affected bulls on thick rubber mats in heated pens also appears to induce a temporary remission of symptoms. The pathology may advance to severe destruction of articular cartilage and massive erosions of the subchondral bone. The author has observed the loss of an entire distal condyle of a femur in one advanced case. Marginal lipping and massive osteophyte formations as well as greatly thickened joint capsules and granulomatous proliferation of the synovial villi are typical features.

One of the geriatric arthritides encountered by veterinarians in small animal practice is canine spinal osteoarthritis (spondylitis deformans). According to Glenney,[2] an inflammation of the vertebral articulations frequently results in outgrowths of bonelike spicules which fuse and result in ankylosis. The incidence appears to be greater in obese dogs and is more prevalent in humid, changeable climates.

As one would expect, farm animals as well as human beings are subject to acute pyogenic arthritides. The incidence and economic importance of pyogenic arthritides in animals have decreased with the advent of wide usage of the antibiotic drugs. Occasionally articular and periarticular lesions in livestock are associated with brucellosis and tuberculosis infection.

Although gout per se is practically unknown in mammalian farm animals, with the possible exception of guanine gout in swine, a nutritional gout or uremic poisoning has been recognized in poultry for many years and is included for completeness of the general discussion. This condition is characterized by deposits of sodium urate, particularly in the kidneys and ureters and, to a much lesser extent, in joints. According to Patterson,[3] the disease appears to be associated with the feeding of excessive nitrogenous concentrates and may reflect a malfunction in nitrogen metabolism, however, the specific causation is presently considered unknown. The disease at present is economically unimportant and appears to have decreased in recent years, possibly because of improved poultry feeding.

In general, the following detailed discussion will be limited to the arthritides of swine, sheep and cattle and will include suppurative arthritis, the rheumatoid-like arthritis of swine and arthritic lesions of brucellosis.

SUPPURATIVE ARTHRITIS

All livestock are subject to suppurative lesions in or associated with the joints. In general this form of arthritis is relatively infrequent, but it does occur under certain circumstances so as to create the impression of a specific

disease entity. Most of these lesions yield staphylococci, hemolytic streptococci or *Corynebacterium pyogenes* on bacteriologic examination; however, a mixed infection is frequently seen

The pathologic changes are varied with the duration and severity of the infection, and the disease is characterized by acute inflammation of the periarticular tissue, hyperemia of the synovial villi and infiltration principally by polymorphonuclear leukocytes The joints are usually markedly swollen, soft and apparently painful. Frequently abcesses are evident in the soft tissue adjacent to the involved joint, and fistulous tracts appear to be a common feature. There is an increase in quantity of synovial fluid, which is usually turbid, purulent and frequently tinged with blood The articular cartilage may be ulcerated, and abscesses are frequently observed in the marrow of the subchondral bone. When bone lesions occur, they are readily detected by radiography.

Pyogenic arthritis appears to be a fairly specific disease entity in swine and foals, and has been termed "infectious arthritis," "joint ill" or "navel ill." It occurs sporadically and may cause heavy losses in newborn pigs and foals. In most cases the infective organism is believed to gain entrance by way of the umbilicus and eventually tends to localize in the joints[4] In affected baby pigs the navel may or may not show evidence of inflammation or suppuration. Occasionally abscesses are found in the livers and spleens of newborn animals with suppurative joint disease

A pyogenic arthritis that also appears to be a specific disease entity in newborn lambs has likewise been termed "joint ill." In this case, the probable entry of the infective organism is through the umbilicus. The disease has also been recognized following docking and castration A nonsuppurative, proliferative joint disease has been reported in lambs, however, the etiologic agent is usually *Erysipelothrix rhusiopathiae*.

Suppurative arthritis occurs somewhat more infrequently in older swine; it has been observed, however, in conjunction with a mild form of cannibalism termed "tail snapping" that is probably related to overcrowding and poor management. The usual picture is one in which a varied percentage of swine in a drove, i e, from a few to as many as 95 per cent, have soft swollen joints The carpal and tarsal joints are most frequently involved concomitant with a correspondingly high percentage of swollen, infected tail stumps The problem is usually satisfactorily resolved by relieving the overcrowding, improved sanitation, separating the offenders—usually the swine with intact tails—and treating the affected pigs with antibiotics

In dairy barns where cows are confined in stanchions, the hock (tibiotarsal) joint is subject to a high incidence of trauma According to Pritchard,[5] suppurative arthritis of the hock joint is a common sequel and can assume

economic importance, since the incidence of joint involvement may approach 30 per cent in a given herd In this instance, antibiotic therapy either parenteral or local usually fails to be beneficial Surgery and the prevention of trauma in affected animals at present seem to be the most effective methods of treatment.

RHEUMATOID-LIKE ARTHRITIS IN SWINE

A joint disease comparable in many respects to rheumatoid arthritis in man occurs naturally in swine, usually as a manifestation of swine erysipelas, an infectious disease caused by the bacterium *Erysipelothrix rhusiopathiae* In this disease great variations occur in the morbidity and the mortality as well as clinical and pathologic manifestations The mortality in a diseased drove of swine on occasion may approximate 30 per cent, while arthritis may develop in as many as 40 to 50 per cent of the survivors. On the other hand, arthritis may occur in a few animals in other droves to as high as 40 per cent, apparently without any of the overt signs of swine erysipelas, i e., a marked febrile response and skin lesions The disease can exist on a farm for years without apparent flare-ups, or it may be present in a low grade form, with a small number of swine showing slight lameness, and go unrecognized until an extensive outbreak occurs. It is conceivable that many animals may acquire some immunity under these circumstances

In the acute septicemic form of the disease the animal frequently develops a temperature of 106 to 108°F within 24 to 48 hours following exposure The range of the normal temperature *per rectum* in a hog is 100 4 to 101 0°F A moderate leukopenia with a monocytosis is usually evident after 72 hours At this time numerous large erythematous areas appear over the body, the animal becomes prostrate and respiration is rapid and shallow If the febrile reaction persists for as long as five days, death is likely to occur. In swine affected to a lesser degree, urticarial or "diamond" skin lesions frequently appear about the third day The fever rarely exceeds 106 5 F and usually returns to normal within three to six days Many of these swine will exhibit a concomitant polyarthritis that frequently becomes chronic.*

The clinical manifestations of arthritis are swollen, painful joints (fig 1), myalgia and varying degrees of stiffness and lameness Initially the joint involvement has a tendency to shift to different peripheral joints and within four to six weeks localize in specific joints and begin to assume a chronic nature The symptoms of arthritis are characterized by remissions and exacerbations Spontaneous recoveries occasionally occur prior to the development of chronic arthritis

The pathologic changes in the joints are essentially proliferative and

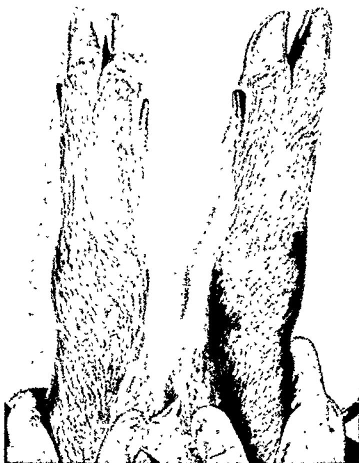


FIG 1 A pair of front legs that were removed from a shoat that was exposed intravenously to *Erysipelothrix rhusiopathiae* three months prior to necropsy Note the marked swellings in the carpal joints

nonsuppurative, with numerous foci of lymphocytes and plasma cells in the synovial villi and adjacent periarticular tissue; marked proliferation of the synovial lining cells and severe hyperemia and moderate hypertrophy of synovial villi are characteristic of the acute joint disease (fig. 2) prior to frank bone pathology. Subsequently, granulomatous proliferations of the

synovial capsule and villi occur with pannus formation, destruction of articulating cartilage (fig 3) and subchondral cellular reactions. Intra-articular fibrous adhesions are a common feature[8,9] in more advanced cases.



FIG 2. Opened arthritic tarsal joint of a pig two and one half months after exposure to *Ery rhusiopathiae* Note the thickened joint capsule and the inflamed and hypertrophied synovial tissue

Roentgenologically, a widening of the intra-articular space may occasionally be detected during the acute inflammatory phase of the disease A narrowing of the joint spaces, generalized demineralization of the bone and osteophyte formations on the joint margins are observed as the arthritis becomes chronic, i e, from the third to the sixth month (fig. 4) Cystic-like rarefied areas (often referred to as "punched-out areas") and erosions of the subarticular bony structures are also characteristic In advanced cases (one year or more) exostoses occasionally become massive, causing obliteration of the joint spaces and resultant bony ankylosis. In some advanced cases, the extensive osteophyte formations at the margin of certain joints and apparent lipping would appear suggestive of hypertrophic arthritis secondary to the primary rheumatoid arthritis, if comparison were to be drawn with the arthritides of man It is possible, though speculative, that the osteoarthritis-like pathology may be related to the fact that arthritic swine will not move their painful joints, ankylosis thus being permitted to develop rapidly [7]

In addition to the pathologic similarities, further parallelisms to the

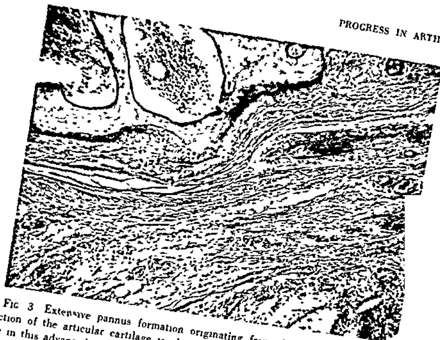


FIG 3 Extensive pannus formation originating from the synovial membrane Destruction of the articular cartilage is almost complete and fibrous ankylosis had taken place in this advanced case (14 months) x85

rheumatoid arthritis in man should include the lowering of the erythrocyte sedimentation rates of arthritic swine with ACTH therapy, and the amelioration of the symptoms of arthritis in swine with cortisone and ACTH treatment [8, 9] Also, pregnancy and experimentally induced icterus, by ligation of the common bile ducts, likewise appear to have a beneficial effect on the symptoms of rheumatoid arthritis in the hog.

It would appear that the chief difference between the disease in swine and the corresponding disease in man is that the etiology of rheumatoid-like arthritis in the pig has been established.[6, 7, 10-13] Wernery[14] appears to have been the first investigator (1937) to describe gross and histopathologic changes in the joints of arthritic swine from which *Erysipelothrix rhusiopathiae* could be isolated. Collins and Goldie (1940) described gross and microscopic pathology of experimentally induced erysipelatous arthritis and concluded it to be identical with the naturally occurring disease.[11]

In general, attempts to reproduce swine erysipelas have met with limited success. Numerous investigators—Ward,[10] Collins and Goldie,[11] Hughes,[13] and Usdin et al.[12]—have found it necessary to employ repeated injections of the organism. In most instances arthritis was produced by these workers without apparent signs of acute swine erysipelas, *i e*, febrile reactions and skin lesions

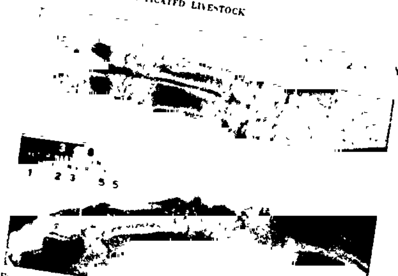


Fig 4 Roentgenogram of the carpus of a hog (anterior-posterior view, top, medial view, bottom) showing bony pathology characteristic of the disease in the fourth month A generalized demineralization of the bone, narrowing of the joint spaces, osteophyte formation and "punched-out" areas are evident

In the initial experiments of Sikes, Neher, and Doyle,[7] 21 swine were exposed to tryptose agar cultures of *Ery rhusiopathiae* that had been isolated from the joint of a hog with chronic arthritis. Injections were made subcutaneously, intramuscularly and intravenously into five hogs in each group and six swine were placed in contact with them. With the exception of moderate febrile responses, which were apparent for only two days in two of the intravenously exposed pigs, the results were negative. A complete herd history was not available on these swine, it is possible they may have obtained some measure of immunity prior to exposure through a clinical or subclinical exposure.

In subsequent experiments we were able to reproduce both acute septicemic erysipelas and arthritis when shoats from herds known to be free from the disease were used. This was possible by means of exposures with highly pathogenic smooth type colonies of *Ery rhusiopathiae*, i.e. isolated from swine that had died of the disease, and by culturing the organism in a semisolid medium which had a reduced oxygen pressure, since the organism is micro-aerophilic. In figure 5 are summarized the results of experiments in which acute septicemic erysipelas and arthritis were produced by a single exposure. The disease was established by seven different methods of exposure.[8]

Method of Exposure	*Number of Swine*	*Mortality from Swine Erysipelas*	*Resisted Exposure or recovered from Acute Disease*	*Chronic Arthritis*
CONTACT	59	15	35	9
SCARIFICATION	22	7	9	6
INTRADERMAL	13	2	6	5
INTRA ARTICULAR	35	6	8	21
INTRAVENOUS	34	20	8	6
INTRAMUSCULAR	16	6	5	5
SUBCUTANEOUS	12	4	6	2
TOTALS	191	60	77	54

FIG 5 A summary of experiments by Sikes et al[8] and Neher et al[7] in which acute septicemic erysipelas and arthritis were produced in swine by single exposures to *Ery rhusiopathiae*

It is apparent that exposure by pen contact was the least severe form of challenge, since 35 of 59 swine (59 per cent) either resisted the exposure or recovered from the disease. The intravenous exposure was the most severe *in that only 8 of 34, or 23 per cent, either resisted exposure or recovered.* The intra-articular method of exposure appeared to be the most effective means of producing arthritis, since 21 of 35 (60 per cent) of the swine developed chronic arthritis It should be pointed out that the arthritis produced in this manner was a systemic disease rather than a local infection, since the overt signs of acute septicemic erysipelas were present and the pathology was by no means confined to the injected joints.

By way of summary, then: roughly 32 per cent of the swine died following various exposures to virulent cultures of Ery. rhusiopathiae, and of the 131 surviving pigs 54, or 41 per cent, developed arthritis.

Because of the consistency with which we were able to produce acute swine erysipelas and arthritis, the next phase of study was designed to evaluate some commercially available immunizing products. It would seem paradoxical that arthritis continues to rank as one of the primary causes for the *condemnation of swine carcasses in federally inspected meat-packing* plants in the United States[16] despite the widespread usage of procedures for the immunization of swine against erysipelas.

Of the 96 swine used in vaccination experiments by Neher et al,[17] 65 were protected against erysipelas (52 with aluminum hydroxide adsorbed bacterin,[15] with virulent desiccated live culture administered concomitantly with anti-swine erysipelas serum) and 31 were exposed as unvaccinated *controls Challenges* were made at various times from six weeks to four months Essentially no difference was observed in the effectiveness of either product, and protection was evident for at least four months following vaccination.

A well defined protection against the acute form of the disease generally was evident in vaccinated pigs challenged intravenously, since the mortality resulting from the challenge was reduced from roughly 70 per cent in unprotected pigs to about 15 per cent in vaccinated animals. The authors concede that the intravenous challenge is an artificial one and certainly a more severe exposure than an animal would sustain under natural conditions, nevertheless, it was employed because lesser challenges—scarification of the skin, topical application of culture, and contact pen exposure—gave inconsistent and inconclusive results The high mortality in unprotected pigs following intravenous challenge appears to be in agreement with the 60 per cent mortality in the intravenously exposed swine reported previously (see fig 5)

Without doubt, the most significant finding was that an unusually high percentage of arthritis resulted in the vaccinated pigs following intravenous challenge The incidence of acute polyarthritis, which was apparent during the first week following intravenous challenge, approximated 90 per cent. Of the 50 protected swine in the various groups exposed in this manner, 36, or 70 per cent, had arthritis two months after challenge, whereas only one of the seven surviving unvaccinated animals challenged intravenously had arthritis two months postexposure.

The unusually high incidence of arthritis in vaccinated (sensitized) swine, a consistent finding in this series of experiments, definitely lends support to the postulate that sensitization may play a role in the etiology of rheumatoid like joint disease following erysipelas infection Further credence was given to this idea when vaccinated pigs consistently exhibited marked anaphylactic reactions at the time of intravenous challenge, in contrast to negative or slight responses in the unvaccinated controls It is of interest to note that following challenge a high percentage of swine developed acute polyarthritis and ultimate chronic arthritis in the absence of the other overt signs of erysipelas, i e, marked febrile responses and skin lesions.

If hypersensitivity is involved in the mechanism by which *Ery rhusiopathiae* causes joint pathology in the pig, it would appear that swine could be sensitized to either the living or dead organism. Using anaphylaxis as an index of hypersensitivity in current experiments,[11] we were able to produce allergic reactions in swine by weekly intravenous injections of 5 cc of heat killed cultures Marked anaphylaxis was evident at the time of the fourth weekly injection (21 days) and subsequently at the time of weekly intravenous injection. After a series of 10 injections the swine were allowed to go untreated for eight weeks When they were rechallenged on the ninth week marked shock reactions occurred The pattern of hypersensitivity was essentially the same in swine sensitized by weekly injections of sterile horse serum, however, when they were allowed a four week rest period after the series of 10 weekly injections, no reactions appeared upon rechallenge on

the fifth week. It was evident that the allergins of *Ery rhusiopathiae* were capable of producing a lasting sensitivity, and it was assumed that the anaphylactic responses that occurred in the vaccinated swine at the time of the intravenous challenge were a manifestation of hypersensitivity to the allergins of the erysipelas organism.

Further evidence that sensitivity is involved in this disease is suggested by the fact that numerous investigators have found it necessary to employ repeated injections of the organism to produce arthritis in the pig.

Recently, Hughes[13] was able to produce the disease in all of 16 pigs without apparent signs of acute swine erysipelas by repeated intravenous injections Only one or two pigs exhibited febrile responses of 104 0 to 104.4 F., and these were exceptional

Similarly, Usdin, Ferguson and Birkeland[12] produced arthritis in seven of eight animals without overt signs of acute septicemic erysipelas, i e., marked febrile responses and skin lesions Sikes, Neher and Doyle[15] produced chronic arthritis in all of four swine which resisted an initial intravenous exposure by giving repeated weekly injections of *Ery. rhusiopathiae*. It is of interest to note that three of the four developed vegetative endocarditis, and death of two of these animals was attributed to these lesions.

Recently, Goldie and Collins,[19] by giving repeated intravenous injections of *Ery. rhusiopathiae*, have been successful in producing in rabbits arthritis pathologically similar to the disease in swine. These authors emphasized that in most instances the exposures were too small (total doses of seven to twenty-eight million organisms) to produce other pathogenic effects Hypersensitivity induced in rabbits by massive injections of horse serum occasionally results in arthritides in conjunction with cardiovascular lesions [20] Pearson[21, 22] recently reported the development of arthritis, periarthritis and periostitis in rats that received adjuvants of allergenic emulsions. It was believed that hypersensitivity was probably the basis for these reactions; however, the possibility of pleuropneumonia-like organisms had not been excluded.

According to Usdin et al.,[12] arthritis is common in horses being hyperimmunized with living cultures of *Ery rhusiopathiae* for the commercial production of anti-swine erysipelas serum.

The production of arthritis in swine through techniques involving repeated exposure to *Ery rhusiopathiae* and, in the present study, by vaccination and subsequent challenge where overt signs of acute erysipelas are absent, would seem analagous to the arthritis that arises naturally in pigs which have never been visibly ill from the acute disease Because of the very widespread distribution of the organism in species other than swine[23, 24] and in swine which are apparently healthy,[25, 26] it would seem probable that under

farm conditions some pigs develop arthritis (*sans* acute swine erysipelas) through sensitization by multiple natural exposures.

Regardless of whether joint disease results from an attack of acute swine erysipelas or develops without the symptoms of acute erysipelas, it is reasonable to assume, according to Hughes,[13] that under natural conditions arthritis arises as a result of a bacteremia. Although *Ery. rhusiopathiae* reaches the joints via the peripheral circulation, we do not know whether the pathology is a direct result of the presence of the organism. Hughes further postulates that if arthritis results from a single exposure the joints may receive repeated doses from some other focus in the body which was set up by the exposure.

The sensitivity theory may explain in part the pathology in affected joints which are apparently sterile. Numerous investigators[4, 11, 13, 27] have reported that only a portion of the typically affected joints of experimental swine are positive for *Ery. rhusiopathiae* on bacteriologic examination. We have been able to isolate the organism from roughly 60 per cent of the affected joints examined from experimental cases in which infection was established less than five months previously. However, isolation of *Ery. rhusiopathiae* from arthritic joints becomes increasingly difficult after this time, even though the pathologic process usually continues unabated. In no instance were we able to isolate the organism after 226 days following experimental exposure.[4]

In the light of recent work it is apparent that vaccination against swine erysipelas may be beneficial in reducing the mortality in outbreaks of the acute septicemic form of the disease, however, it is conceivable that this p[...] cedure may contribute to, rather than solve, the arthritis problem.

BRUCELLOSIS AND ARTHRITIS

Brucellotic osteomyelitis and spondylitis (one of the lesions associate[d] with undulant fever) has been recognized in man for many years. As o[f] 1949, according to Lowbeer,[23] 150 papers had been published on this aspect of the disease. Brucellosis (contagious abortion) was first described in cattle by Bang in 1896. Although the disease presently is of great economic importance to livestock raisers, it probably assumes greater importance from a human health standpoint. Arthritic lesions in the bovine that result from brucellosis infection are considered rare, whereas in swine a spondylitis similar to that of brucellotic spondylitis of man is not infrequently associated with the disease.[21]

Brucellosis (infectious abortion) in swine was first recognized in the United States in 1914 by Traum, who recovered from aborted fetuses an organism of the genus *Brucella* which was later named *Br. suis*. Feldman and

Psychosocial Factors in Rheumatoid Arthritis: Considerations for their Clinical Management

by H M. Margolis

IT IS IMPOSSIBLE, OF COURSE, to delineate the specific role played by psychologic and emotional factors in a disease such as rheumatoid arthritis, when the disease's etiology is unknown and its pathogenesis so obscure. Our concept of rheumatoid arthritis, developed as a result of clinical observations, includes the clear impression that stresses of various sorts contribute to predisposition, onset, and perpetuation of this disease. In addition to whatever genetic predisposition may exist,[1, 2] stresses related to infection, trauma, the patient's social environment, or personality reaction mechanisms may disturb physiologic adaptation, contributing in some way toward those pathologic mechanisms which produce this disease.

The symmetrical pattern of joint involvement has suggested to some a possibly neural origin for rheumatoid arthritis. More impressive is the fact that emotional shock, worry, and anxiety have at times been closely related to the onset and exacerbations of the disease. We have seen the precipitous onset of widespread arthritis shortly after an explosive emotional shock. With the least prodding, and frequently without it, the patient himself is likely to express a belief in the close relationship between emotional stress and the onset of his arthritic disease.

Studying fifty patients with rheumatoid arthritis, Cobb, Bauer and Whiting[3] found a close chronologic correlation between stress situations of grief, poverty and family worry and the attacks of arthritis in no less than 66 per cent, suggesting that such stress, even at a conscious emotional level, to which the patient cannot make adequate adjustment, may be a formidable factor in "preparing the soil" for arthritis.

PERSONALITY CONFIGURATION

King[4] has recently presented an excellent critical review of the literature on psychologic and social factors associated with rheumatoid arthritis, and he has suggested certain fruitful areas for further research. Our own day by day experience with rheumatoid arthritis patients has convinced us of the existence of a personality pattern, in general so characteristic that we may regard it as a possibly meaningful common denominator in the disease picture. Obviously there are significant variations in individual cases, both qualitatively and in degree. In some, the personality structure shows rela-

tively little deviation from "normal", in others, the psychoneurotic structure is glaringly apparent. In still others, the basic personality structure is so obscured by a rigid facade that only the most superficial insight can be obtained without detailed study of the person.

Perhaps the most obvious feature of the arthritic personality is a rigidity of manner and bearing, which appears to symbolize both his inner emotional inflexibility and the subsequent character of the organic changes in the joints. The involuntary spasm of the musculature, which aims at protecting the painful joints, appears as the counterpart of the general behavior, which aims at shielding a difficult or inadequate adaptation to life situations. Arthritic patients are generally quite inaccessible and resistant to direct psychoanalytic investigation. Their psychologic defenses appear as if encased in plaster. What insight one may gain into the mechanisms of their personality constitution is achieved only by chipping away at its encasement slowly and adroitly over periods of time, as opportunity allows in the course of general management of the arthritis.

Ludwig[5,6] has described the depressive trends, marked dependency, insecurity and "severe blocking of the external expression of emotion, with internalization of feeling" in the adult patients he studied. A similar pattern of "strong control of all emotional expression" was noted through psychoanalytic observation of a group of adult patients by Johnson, Shapiro and Alexander.[7]

Blom and Nicholls,[8] studying a group of children with rheumatoid arthritis, were likewise impressed by the patients' "inability to express feelings" and the "infantile personality structure, growing out of a long sustained conflict situation where the outstanding element is the inability of the child to achieve separateness from the mother." They felt that the emotional factors in the group of rheumatoid children bore some fundamental relationship to the disease, more as a precipitant than the cause of the disorder. In a later study[9] their evidence showed that the psychoneurotic structure of these children antedated the disease and did not result purely from an overlay of invalidism in those who had been ill for a long time.

Quite unlike certain other psychoneurotic individuals, the arthritic is literally afraid of his emotions, shunning every opportunity to communicate his feelings even to his physician. When his defenses falter or fail altogether under severe pressure of pain or anxiety, the patient may betray the full depth of his insecurity and anxiety, but generally not for long. For the ego constitution of the arthritic is trained to clamp on the lid, and then we see again the rigid stoical facade, the mobilization of a well trained compulsive drive toward goals that seem to him so essential and that are often so unattainable. This compulsive drive may be evident as far back as one can trace the history of these patients. In the most active phase of the arthritis

process this trait may pose a real obstacle in treatment, for instead of permitting rest or immobilization of inflamed joints, which may be so necessary, the patient pleads that he be allowed to "fight" his disease with valor. Regardless of distress from pain, he wants to "keep going," as he says, "to keep the joints from stiffening up."

These personality attributes of the arthritic, so clearly reflected in the character of the organic manifestations in the joints, have long impressed me with the possibility that the arthritis may actually be a somatic verbalizaion of the patient's drive to attain some readjustment of a failing equilibrium. There may actually be a relatedness between the rigid personality structure of the individual and the muscle spasm and ultimate rigidity of joints expressing the most obvious organic structure of the disease. This hypothetic correlation points at least to the necessity for exploration of some basic dynamic drives of the personality in order that we may perhaps better understand the meaning of the arthritic process. I am convinced, in any case, that viewing the total individual—his psychic physiology, as well as his pathologic anatomy—has given us a view of the patient and his disease which has helped materially in carrying out the complex regimen of treatment the arthritic requires.

PSYCHOSOCIAL FACTORS

Cleveland and Fisher,[10] who studied the behavior and unconscious fantasies in 25 male patients with rheumatoid arthritis, described the person as "an overtly calm individual who rarely expresses or consciously feels anger However, covertly he seems to be containing a large amount of hostile feelings. Aiding him in his defense against hostile expression is his unique body image—the arthritic thinks of his body as a kind of hollow container filled with uncontrolled, fluid material and surrounded by a hard, impenetrable surface. Inconsistent parents seem to have supplied the original model for this body image. Father is described by these patients as having been inconsistent in his expression of anger, being ordinarily a calm, easy-going person, but one who burst forth irrationally at times Mother is remembered as an overtly moralistic and self-sacrificing person, but on the projective tests she is also revealed as having been a prohibiting and seductive figure. The arthritic patient attaches unusual significance to his body and is unconsciously desirous of exhibiting his physique. Overtly he denies his exhibitionistic desires and in fact complains of his shyness and inadequacy."

McLaughlin,[11] studying the emotional reactions of rheumatoid arthritis patients to ACTH, found, among other things, that remembrance or nonremembrance of dreams was associated significantly with improvement or lack of improvement on ACTH. Commenting on this fact, King[4] points out that "many psychologists feel that remembrance or nonremembrance of

dreams is related to leniency or severity of emotional control by the ego, especially of unconscious material." He postulates that "patients who did not remember their dreams had relatively more repression than did patients who remembered them. They also had more intractable rheumatoid arthritis in that it did not yield to ACTH therapy."

In a composite view of the arthritic's early life situation we have seen in the main an environment seldom conducive to emotional security. Rheumatoid arthritis appears to be more prevalent in the economically depressed strata of the population, but there is often a poverty of *emotional* security even when it occurs in families that are otherwise secure. Many patients present a picture of childhood beset with problems of adjustment. They speak of economic stress, or recurrent illness in the family, or they describe homes shaken by the death of one or both parents, or by divorce, or by domestic conflict. Only six out of forty-two patients studied by Booth[12] were not confronted by a special problem of adjustment dating from earliest childhood.

Deprivation of emotional security is often accompanied by an overstrict disciplinary code. In childhood these patients are often subjected to harsh discipline and overemphasis on show of decorum. Any breach, such as lack of punctuality, cleanliness, neatness, or direct show of emotion may provoke derision or outbursts of censure, sometimes compensated for by overindulgence or oversolicitude. Thus, "Life with Father" becomes an exercise—a need to be constantly on guard, the earliest origin perhaps of the rigid stance and bearing of the potentially arthritic personality.

I recall a man with a hand-washing compulsion and rheumatoid arthritis of the spine whose emotional development in childhood was rigidly restricted by the family environment and personalities. He had a rather masklike expression and a rigidity of stance and gait that seemed to express not only the organic manifestations of his arthritis but probably also the repressed aggression toward an environment which crippled him emotionally, if not physically. Although there was so much rigidity of the personality that one was unable to obtain direct data from which to draw any detailed psychodynamic picture, there was sufficient collateral evidence to suggest that the arthritic and personality disorders in this case were not unrelated.

Thomas[13] found a fairly severe emotional disturbance of one kind or another, which had been present before any sign of arthritis, in all of thirty-one patients he interviewed. He traced a consistent pattern of various types of neurotic behavior over a period of years, the subsequent development of an unusually severe conflict, and the appearance of arthritis in the midst of this struggle. The sexual adjustment of most of these patients was inadequate. Booth[12] felt that because of a neurotic emotional maladjustment they were unable to establish a harmonious and unstrained relationship between themselves and their environment. An outstanding feature was their difficulty in

making satisfactory sexual or matrimonial adjustment. Psychoanalytic study[7] of a group of female patients revealed the extent and degree of interference with fullest psychosexual development among them. Such findings indicate not only the degree of repression of a basic dynamic energic drive but suggest also the concomitant anxiety that occurs when these repressed libidinous drives do not find channels for satisfactory expression. Although we find evidence of satisfactory sublimation among many arthritics through various channels of creative and satisfying activity, some arthritics merely divert inordinate stores of emotional energy as well as a great deal of muscular activity in sports or hard work. The female patients carefully studied[7] have also shown a tendency toward bodily activity, especially outdoor and competitive sports—activities, it should be remembered, constantly operating on the muscle-joint mechanism. When the channels for expression of such highly charged drives are blocked by difficulties which disturb interpersonal relations in the environment or by physical incapacity, much of the energy is channeled back into the organism, producing states of emotional and muscle tension It has been suggested[4] "that physical activity gives some form of libidinous satisfaction to these people, except that their drive to be active is in excess of their capacity to find useful channels for the release of their energy This interest and participation in muscular activity can be thought of as a form of sublimation, or a means of relieving tension, perhaps tension due to unexpressed aggression, with the individual more susceptible to arthritis when the sublimation is no longer available or effective"

ILLUSTRATIVE CLINICAL CASES

1 Miss B., who came to us 17 years ago, at the age of 59, has suffered from a severe, generalized arthritis for twenty-nine years. She is an intelligent, aggressive, resourceful woman, with a prominent masculine component. She was born into a family of eight. There was considerable sibling rivalry The domineering father who "never asked for anything twice," demanded action and perfection and died of a heart attack at fifty-four. Despite severe deformities of many joints, especially in the hands, and despite repeated exacerbations of the arthritis which required confinement to bed periodically for weeks or months at a time, this patient has held a responsible position through all these years as head bookkeeper of a large firm.

The destructive influence of her hostility and feelings of insecurity were clearly revealed in one conflict she maintained at her office with a subordinate employee, whom she unconsciously feared as a rival for her job He was a young man, expert in his job and almost indispensable to our patient. But she could not tolerate his occasional tardiness in the morning, his going out to the roof for "sunning on his lunch hour." These actions disturbed her sense of duty, her overwhelming compulsion to be "always doing something."

There was overt hostility between the two. "When he would get mad," she said, "I could feel a sense of trembling tension start in my feet and spread all the way up the muscles of my body." She sought a showdown. The "boss" would ask her to be tolerant, explaining that he couldn't easily replace this man, whereupon the patient would threaten to resign. She would be told she was badly needed and asked to stay on. "As I left that conference," she said "I knew the boss really wanted me to stay, that he didn't just tolerate me because he didn't have the heart to dismiss me." Her security bolstered again, her courage was sustained and she would go on with her work.

At times, she could manifest signs of aggression and express the hostility which she tried so hard to control. Perhaps the capacity she retained for release of feeling and tension accounted in part, at least, for the relatively benign course the severe arthritis has followed in her case to this day. On one occasion, early in our contact, Miss B.'s hostility verged on a state of actual belligerence. Although she had managed relatively well, considering the severity of the disease, she was resentful of fate, of all her physicians, and was more than a little suspicious of us. She wanted to know without equivocation how much benefit we could promise, how long it would take, and how much it would cost. Instead of retaliating, as she had expected, we met her demands with sympathetic understanding. Realistically, we reassured her that something might be done to help her with improvement or restoration of joint function, but emphasized that the irreparable physical damage must be accepted as the liability that it is. As to the length of time required, we indicated that we cannot cross bridges before we get to them, that the expense would be adjusted to her means. Instead of the authoritarian attitude she probably expected and for which she had girded herself, we tried to create a relationship based upon mutual teamwork to be devoted toward her recovery. Under such conditions we have been able to carry out successfully to this day a rather exacting program of treatment, always bolstered by psychotherapeutic measures which aim at maintaining the patient's self esteem, at reducing the destructive influence of her hostility and feelings of insecurity.

Without going into details of the psychodynamic structure, we nevertheless observe here an example of early emotional trauma and want, the insecurity it created, the compensatory compulsive drive, the muscle-joint tension it induced, the constant flow of anxiety, the hostility it engendered, the depleting effect of a psychoneurotic life long struggle, its culmination in arthritis, and the possibly reciprocal relationship between the disease and the personality structure. We need hardly add that the many purely physical measures of treatment, which were so essential, could hardly have been employed without therapy based on some understanding of the personality.

2 Another more malignant course of the disease was observed in a man (Mr. W.) who was born into an environment of economic poverty and deep emotional insecurity. His physical development paralleled his social and emotional stature, for just as he was stunted in normal emotional growth, so was he slight in build and always frail. The patient remembered his father, a foundry workman, as nearly always drunk, always quarreling at home, yet demanding obedience and punctuality, and sadistic in the punishment he meted out for infraction of his rules. When the patient was eight, the father, at the age of thirty-two, "shot his head off." Three months later the paternal grandfather did the same thing Two years later the mother had to send the six children, of whom the patient was the oldest, to various orphanages. The patient says, "I loved the orphanage awfully much. I always had something to eat, did what I was told and was treated fine. But at sixteen I had to leave, they didn't keep anyone beyond sixteen." He went to work in a printing establishment and went to live with his maternal grandmother, but "didn't like it there." Six months later he went to live with his mother. After a year, he took a job in a candy factory, but "didn't like having to keep up with the machine," which he described as if it were a cruel disciplinarian. He drove a truck for a few weeks and then took a job as "stationary engineer" in a railroad roundhouse After three and one-half years, the depression came and the job didn't appear too secure, so he obtained more steady work hauling building equipment "When they hired me," he says, "they didn't think I could do the work, but I fooled them. . . . Singlehanded I would unload bathtubs, radiators, and furnaces . . I worked hard, often twelve hours when I was on a long trip, but I liked the job." In retrospect, he realized that he was always tired, that he worked "too much, too steady, without vacations"

Between the age of seventeen and eighteen he was afraid to be out with people. "I felt as if something might happen to me, that I might fall or die So I would go around streets where there were no people" At the age of twenty-five, he married a rugged, hard working, frugal German girl who, in her physical build and demeanor, was the mother substitute A few months later the wife took over a successful grocery business and the patient plunged toward the success he sought. He continued his former job, but also helped in the store. "Early in the morning I would deliver the beef to the store and then, after a short rest, go to my regular job." Eventually he gave all his time to the store. At the age of thirty-nine, with energy dwindling, "I became lazy and sickly," and two months later abruptly developed a severe, generalized rheumatoid arthritis After some desultory attempts at treatment by physicians, osteopaths, and chiropractors, he was referred to us by his physician for a review of his problem and recommendations for management.

The man was seriously ill, the widespread arthritis was associated with systemic debility.

A program of management, including rest and protection of the joints against development of deformity, was outlined in detail. The necessity for scrupulous adherence to it, if the activity of the disease were to be arrested, was emphasized. After a short period of treatment, however, during which the patient insisted on continuing at his business, his condition deteriorated. He went to Arizona in search of a "cure." Upon his return he was worse. All the joints had developed marked destructive changes; the knees and spine had become deformed in flexion. Again, a comprehensive program of management was urged. Despite mounting activity of the inflammatory process, however, the patient rebelled at staying in bed. He insisted on what ever treatment could be given while he continued at work, at least part time. As might have been expected, such a course met with increasing failure. When the patient was referred to us again four years later he was completely incapacitated by advanced destructive changes in nearly every joint, with profound deterioration of his general state. Most joints were completely fused. Because of ankylosis at the jaws, the mouth could barely be opened. The general appearance was that of severe cachexia. There was manifest anxiety and, at times, guardedly expressed hostility directed toward his doctors, the members of his family, the Arizona climate. He felt himself in a state of defense against a hostile environment which he was still determined to subdue. Despite this almost hopeless state, the patient was more determined than ever to launch aggressively upon any course of treatment that might be suggested. He was hospitalized, but every attempt at stemming the tide of his destructive disease failed. He was doomed to lifelong invalidism by complete fusion of nearly every joint and by the most bizarre distortion of limbs. The only constructive accomplishment consisted in surgical resection of the temporomandibular joints to permit opening of the mouth for feeding.

The patient was then transferred to his home, a comfortable home in the country where, for many years, until he died, he was cared for by the wife's mother and father, who lived in the house next door. The wife managed the store successfully and nursed the patient at night. An ingenious set of contraptions had been devised by the family and erected around the patient's bed; these permitted him to rule with omnipotence. I would see him from time to time, when he issued a command to the family for my review of his situation. The slightest tug on a rope sounded bells which called on whatever member of the family was in attendance. And woe unto him who did not respond promptly or adequately. When his dependent needs were to be satisfied he could be a veritable despot; at other times he seemed happy, carefree, amiable, describing an affective state of peace that appeared actually ludicrous in relation to his nearly mummified physical state. The

only vestige of the previous ambivalence between his dependent and aggressive wishes was his periodic "check-up on newer advances in arthritis," through which he still looked for rehabilitation some day.

INTERPRETATION OF CLINICAL DATA

The only peace this patient had found, it seemed, was a shabby compromise, but with the emotional and physical resources at his command, which hampered every effort at adequate management of the arthritis, it was the best he could achieve. Whether this patient was exceptionally vulnerable to the destructive influences of his disease through inherent predisposition or some extraneous effects, it is impossible to say. One wonders, however, whether the basic emotional striving of this patient might not have utilized the psychologic mechanisms he employed to achieve a certain goal. It is possible that every step in his behavior, verbalized by his somatic manifestations, was really a purposive, though unconscious, expression of this individual's attempt to achieve some sort of new equilibrium, some sense of "being," of validity, and "security."

We may hypothecate, though it is by no means established, that in the case just cited, which is merely the ultimate expression in terms of severity of a basic psychobiologic reaction occurring in many rheumatoid arthritics, the basic hunger for security and love, resulting from earlier deprivation, led to compulsive drives which appeared to be aimed at achievement of an avowed goal The "on-guard" rigidity of the organism, however, its incapacity to find satisfaction in its relations with society, including the interested family doctor in this case, was not compatible with the smoothest functioning of the organism The frictions that developed must have been depleting, for there was a dynamic drive with the throttle wide open and the brakes rigidly clamped No wonder the patient found himself at an increasing disadvantage, pulling ahead under such circumstances, with energy dwindling, with breakdowns in resistance culminating in the development of the full-blown arthritic disease. Even then, Nature's attempt to stop the patient for a new attempt at integration was frustrated, because the compulsive drive was too highly charged. So often the arthritic patient cannot heed or accept the signs of his dependency, actually accentuated by his disease, and is forced to move on as long as he can, despite serious arthritic involvement, until complete destruction of joints, deformities, and ankylosis force him to a dead stop

It is perhaps important to appraise the reaction pattern at this point, especially as seen in some patients in the most severe forms of the disease, for it appears to us revealing For after all the struggle to move, to keep going no matter how much it hurt, with complete and irrevocable invalidity, there descends at last a certain peace, hardly resignation to the seemingly in-

evitable, that appears to describe the innate need of this organism to achieve regression to an infantile dependence, a state in which the responsibility for the satisfaction of every basic need is met by someone else. The utter physical incapacity then becomes the useful instrument for reestablishing the long missed infantile dependence and omnipotence.

Admittedly, the interpretation of this series of events is not incontrovertibly documented by objective data, so that one may accept it today without reservation. Indeed, more extensive and detailed investigation of this aspect of the problem is essential but, because of the inherent difficulties of such research, has been relatively neglected.

The picture I have just cited is a gloomy one, indeed, but it need not turn out so, and fortunately, it does so only rarely. With help, most patients with rheumatoid arthritis employ their psychologic defenses more constructively and, especially in the face of the obstacles introduced by the painful and debilitating disease, demonstrate a remarkable capacity for adaptation to the manifold psychosocial and physical problems they face for years or a lifetime. But to accomplish this, we, who treat the arthritic patient and seek to modify the course of his arthritis, must try to learn not only the many physical factors that may contribute to the genesis of the disease but also the personality constitution, the emotional strivings and needs of the given person with arthritis.

It might be said that the characteristics we have described do not present a precisely defined personality profile that many features are found also in patients with peptic ulcer, ulcerative colitis, and hypertensive cardiovascular disease, that a specific psychodynamic structure has not been consistently revealed. These criticisms are valid, human personality characteristics cannot be neatly compartmentalized for the sake of convenient, distinctive labels, and opportunities for intensive personality studies of arthritics need to be extended.

In rehabilitation, Lowman[14] has observed that "the psychological timbre of the rheumatoid arthritic is a major force in determining success or failure in attainment of goals. ... We have become acutely aware of this factor and have intensively studied the problem. ... It is felt that in the course of a progressive disease such as this ... the psyche becomes more or less inundated by the constancy, the hopelessness, and the helpless frustration to which it is subjected. The result is an exhaustion of psychological economy and a reversion to passivity and dependency. It would appear that the degree to which the latter tendency crystallizes depends not upon a preexisting specific rheumatoid personality but rather upon the soundness of the patient psychologically prior to the onset of his arthritis and upon the tempo of the disease process.

"In the course of studying this almost inevitable passivity and dependence

among these chronic cripples, we have found that in many patients it has been a reversible process . . . We have been interested, therefore, in trying to sort out the common denominators in these successful rehabilitees so that we might identify the assets they possessed that permitted them to carry on successful programs while others could not accept or work toward similar goals."

The relation of psychologic factors to the genesis of rheumatoid arthritis is by no means proved, however, or universally accepted. In an excellent investigation of 532 patients with rheumatoid arthritis compared with an equal number of controls of identical age, sex and civil state, each person was asked "a series of questions relating to events occurring before the onset of arthritis that might be expected to produce psychological disturbances."[1] Since the analysis showed "no significant difference between patients and controls in the occurrence of these events," it seemed logical to conclude that "the widely held belief that psychological factors play an important part in the etiology of arthritis is not borne out by this controlled investigation if this view is based on a higher occurrence of such factors in patients as compared with the rest of the population." Such statistical evaluation, interesting and valuable as it is, does not, however, supply the important link of psychodynamic interaction. As Brown[15] stated in discussion of a similar problem, "The danger of oversimplified single-variable analysis cannot be underestimated . . . The problem of psychosomatic differentiation involves more than statistical balancing and measuring through strict abstraction. One must deal with problems of quantity, which takes us into the qualitative field in such a way that greater or lesser amount of a variable is directly related for its eventual weighting to other elements in the constellation. . . . Problems of emphasis must be considered, strategics come into play, and coping mechanisms must be considered. The patterns may be as alike as an original Rembrandt and a good copy by a bright art student, but the subtle and unquantifiable nuances establish the difference between the two . . .

"It is not the presence or absence of test-derived categories which is crucial . but the manner in which they form themselves into constellations in the total test battery. The static facts of mental illness were observed here and there long before Freud, but it required the patient psychodynamically attuned evaluations of data to discover and utilize strategic facts. . . . The statistical approach in psychosomatic medicine, if used alone, deals primarily with static facts."

In describing the possible psychogenic background of rheumatoid arthritis by citing specific instances in individuals with grossly psychoneurotic personality structure, I did not intend to imply that I regard such emotional and personality influences as the only etiologic factor involved Committed to the

principle of multiple causation in disease, one can no more accept a purely psychologic origin for rheumatoid arthritis than one can accept the idea that any other single etiologic factor is likely to be the sole cause of this disease. On the contrary, we might regard chronic arthritis as the total expression of a protracted struggle for adaptation to a convergence of a variety of factors inherent susceptibility, depletion of general "resistance" by endogenous factors related in some cases to emotional stress (from anxiety, repressed tension hostility)), further depletion by various types of environmental stress, such as fatigue, exposure, infection, or nutritional deficiency. The various elements in this equation are likely to vary quantitatively in different patients. This idea is supported by clinical experience which, though always suggesting the coexistence of a number of possible stressful factors, may emphasize the predominant influence of infection in some cases, of heredity in others, and of psychogenic influences in still others. To phrase the situation another way, we may say that if emotional stress contributes to the precipitation of rheumatoid arthritis, it may perhaps do so by depleting the patient's normal defenses, so that his capacity for adaptation to usual environmental stresses is lost. When this has occurred, factors which the individual might have tolerated under other circumstances may become distinctly pathogenic.

It may be that the experimental data of Selye,[18] dealing with the physiologic response to stress, have some bearing on our problem at least they point to one physiologic mechanism through which emotional stress may act in depleting the patient's defenses. May we then conjecture that the onset and exacerbations of arthritis, adduced by some to "hypersensitization" phenomena, may at times actually be the result of "sensitization" to environmental stresses, or to products of a deranged endogenous metabolism induced, in part at least, and perhaps in particular individuals, by deleterious emotional influences arising from the patient's stressful mode of adaptation to life situations?

SOME PRINCIPLES OF CLINICAL MANAGEMENT

Perhaps by recognizing the personality features of these people long before the arthritis has developed, and by modifying them, we may actually succeed in some cases in preventing the development of the structural disease. For preventive medicine, disability and rehabilitation are intimately dependent upon personality integration these never stand apart.[19]

When the psychodynamic background of the rheumatoid arthritic patient is understood, it becomes obvious how necessary it is for the physician to communicate a sense of security to the patient in the treatment situation. In the medical team often required for the management of rheumatoid arthritis the internist is called upon to integrate a situation that could be

chaotic. Alone or, when possible, with the aid of the medical social worker, he may discover factors blocking the acceptance of recommendations for medical care, he may act as the crutch on whom the patient may lean with confidence, he may allow the patient to vent hostility, thus reducing emotional tension that might otherwise be dammed back into the sick organism, he may help the patient express his fears about his disease, and its effect on his future. Our social worker has also served as an effective liaison for the reticent, sensitive patient in the trying experience of establishing rapport with the physicians, some of whom may represent to him omnipotent and authoritative persons to be evaded The case worker has offered constructive help as the individual becomes ready to move ahead step by step when his physical activity is increased, when he becomes capable of leaving for short walks, when the process of rehabilitation is extended, when he is allowed resumption of employment, or is seeking a new vocation or a new job.[17]

Deprivation of essential income engenders additional feelings of insecurity and concern which the family, or the patient, may translate into uncooperativeness or hostility. Or they may embark on frantic and aimless wandering from doctor to doctor, or trial of one recommended panacea after another, incurring impossible financial burdens and added emotional stress when they are least capable of bearing them. The physician and the social worker may help with many such problems of family adjustment.

Delving for deep insight into the dynamics of the patient's psychologic and emotional problems can be hazardous, in the rheumatoid arthritic patient it is so difficult that it should be attempted only by the psychiatrist Such patients should be carefully screened for referral on the basis of their potential resourcefulness for attaining personality reintegration. Although the psychotherapeutic aspect of management is no less important than the physical, the patient with a crippling arthritis is likely to resent any suggestion of a "psychic" component in his illness He has no anxiety with regard to his personality problems; he is too deeply fixated on his physical incapacity. Should he recognize the existence of an emotional conflict, he would very likely place the blame for it squarely on the arthritis In such circumstances, the internist aware of the total constellation which constitutes rheumatoid arthritis can, in most instances, be of constructive help in the *total, comprehensive* care of his patient It is well if the psychotherapy of the internist is based on more than intuition

With experience, we learn to anticipate the many questions that perplex our patients, the doubts that arise as to the efficacy and the wisdom of what is being done, the anxiety about the future, and so on. The wary physician will guard against exaggerating the passive dependence of his arthritic

patient. A relationship established for constructive support of the patient may also be utilized at an appropriate time for encouraging increased activity and responsibility. Compulsive drives with physical overactivity and rebellion against their limitation in the course of treatment, when used by the patient as a defense against his dependent attitudes, must be handled with understanding of their meaning. Restriction of this outlet for aggression too severely or prematurely may make matters worse, just as premature loading of responsibility may prove intolerable.

In actual practice we have found that the personality reactions of the arthritic patient are often amenable to varying degrees of constructive reintegration. Since management of chronic arthritis often requires a long time we are challenged to make the best use of this long and close interpersonal relationship not only for restoration of integrity of joint function but also for restoration of smoother functioning of the individual. Obviously the results achieved will not depend on us alone, for the constitution of the patient and his environmental milieu are large determinants.

In prognosticating the probable outcome one must be realistic, one must avoid exaggerated predictions of what may be accomplished. The problem is not an easy one. But despite all the physical liabilities that go with rheumatoid arthritis, such patients may have retained worthwhile, perhaps invaluable, inner resources which they may somehow be induced to use to the greatest advantage, as Professor DaCosta and Clarence Day used their gifts, one as a great medical teacher, the other as a tolerant social satirist.

References

1. Report by the Scientific Committee of the Empire Rheumatism Council. A controlled investigation into the aetiology and clinical features of rheumatoid arthritis. Brit. M. J. *1*: 799, 1950.
2. Margolis, H. M. and Eisenstein, V. W. Twins as biologic controls in the study of human constitution. An additional approach to the study of clinical medicine. Ann. Int. Med. *6*: 1489, 1933.
3. Cobb, S., Bauer, W. and Whiting, I. Environmental factors in rheumatoid arthritis. J.A.M.A. *113*: 668, 1939.
4. King, S. H. Psychosocial factors associated with rheumatoid arthritis. An evaluation of the literature. J. Chron. Dis. *2*: 287, 1955.
5. Ludwig, A. O. Emotional factors in rheumatoid arthritis: their bearing on the care and rehabilitation of the patient. Physiotherapy Rev. *29*: 339, 1949.
6. Ludwig, A. O. Psychogenic factors in rheumatoid arthritis. Bull. Rheumat. Dis. *2*: 15, 1952.
7. Johnson, A., Shapiro, L. B. and Alexander, F. Preliminary report on a psychosomatic study of rheumatoid arthritis. Psychosom. Med. *9*: 295, 1947.

8. Blom, G E, and Nicholls, G Emotional factors in children with rheumatoid arthritis Am. J Orthopsychiat. *24*, 588, 1954
9 Blom, G E, and Long, R T · Psychosomatic study of children with rheumatoid arthritis Annual Meeting Am Rheum Assn, Chicago, June 8, 1956
10 Cleveland, S E, and Fisher, S. Behavior and unconscious fantasies of patients with rheumatoid arthritis. Psychosom Med *16*. 327, 1954
11 McLaughlin, J T, Zabarenko, R N, Diana, P B, and Quinn, B. Emotional reactions of rheumatoid arthritics to ACTH. Psychosom Med *15*: 187-199, 1953
12 Booth, G C. Personality and chronic arthritis J. Nerv. & Ment. Dis *85*· 637, 1937.
13 Thomas, G. W *Psychic factors in rheumatoid arthritis Am J Psychiat 93*. *693*, 1936
14 Lowman, E W., Lee, P R, and Rusk, H A.: Total rehabilitation of the rheumatoid arthritis cripple. J A M A *158* 1335, 1955
15 Brown, F. *In* Streitfeld, H S Specificity of peptic ulcer to intense oral conflicts Psychosom Med *16* 325, 1954
16 Selye, H. The physiology and pathology of exposure to stress. Acta Inc, Montreal, 1950
17 Margolis, H M and Mendelsohn, H The medical social case worker in "private" medical practice *J A M A 161 309, 1956*
18 Cockerill, E and Margolis, H M The concept of disability J Chron Dis *3*, 167, 1956

Juvenile Rheumatoid Arthritis

by Bernard M. Norcross, L. Maxwell Lockie and Colin C. MacLeod

INTRODUCTION

IN 1897, STILL REPORTED 12 instances among 22 children with rheumatoid arthritis who displayed such unusual findings that he postulated the existence of a distinct disease, now known by the eponymic term. Girls were more frequently affected than boys, with the onset of the disease occurring before the second dentition. In eight of the twelve patients symptoms appeared within the first three years of life, the earliest case developing at ten months of age. The onset was usually insidious; fever was continuous at a low level or intermittent and not related to joint symptoms. Profuse sweating and mild anemia were common. The characteristic physical findings were retarded physical growth, marked muscle wasting and absence of joint pain. The joints most frequently involved were the knees, wrists and cervical spine. Still attached much importance to enlargement of the lymph nodes and to splenomegaly, as well as to the absence of osseous and cartilagenous changes. "Still's disease" is prone to involve serous membranes, pericarditis and pleurisy were present at autopsy in three of Still's original patients. These findings constituted the chief argument for establishing a new clinical entity.

Although Still[1] merits recognition for the association of visceral and constitutional abnormalities with rheumatoid arthritis in children, he inadvertently laid the basis for much of the confusion regarding the course and prognosis of juvenile rheumatoid arthritis. It is difficult to believe that there is a valid reason to consider "Still's disease" as a separate entity. Bone and cartilagenous destruction occur, there is no fundamental difference in the anatomic or pathologic lesions of "Still's disease" and rheumatoid arthritis, and many gradations of severity of the disease develop in the child in recurrent attacks. Moreover, one of the most distinctive findings in juvenile rheumatoid arthritis, i.e., abnormal bone development, is merely the effect of the disease upon the growing epiphyses. Only a few large series of patients have been reported, so that marked discrepancies exist in the knowledge of the course and the effects of the arthritis in the average patient. It is hoped that some of these differences will be clarified in this study.

INCIDENCE

If one judges by the paucity of large series of juvenile patients in the medical literature,[2, 11, 13] it might be reasonable to assume that this disease



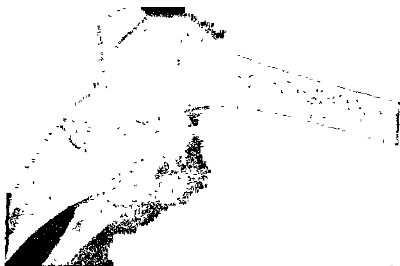


FIG 1 Roentgenogram of the knees of an 8 year old boy, illustrating "woolly" subchondral bone outgrowths of early rheumatoid arthritis

is rare. However, it is our experience that rheumatoid arthritis in children is more frequent than previously believed. Three reports place the incidence of juvenile rheumatoid arthritis between 4 and 4.9 per cent of all cases of this disease.[2, 6, 13] In Sweden only 0 7 per cent of 16,000 patients who received

medical treatment for rheumatoid arthritis were under the age of 15 years.[4]

In a twenty-year period (1935-1955), 80 patients with juvenile rheumatoid arthritis were observed by us, an incidence of 2.7 per cent of all cases of rheumatoid arthritis. Because this group includes ambulatory office patients as well as hospitalized patients, it is believed that it represents a faithful picture of the average incidence. The results set forth herein are based upon the course of the disease in 62 patients who have been studied periodically for more than seven years.

SEX AND FAMILIAL INCIDENCE

In universal agreement as to the greater frequency of juvenile rheumatoid arthritis in the female sex, most authors have calculated the ratio to be two to one,[2, 4, 6, 12, 13] a value which coincided with 41 females and 21 males in our series.



Fig. 2. Anterior-posterior views of the knees illustrated in figure 1

A familial occurrence of rheumatoid arthritis or rheumatic fever has been postulated in these patients. Values as high as 20-30 per cent[2, 5, 8] and as low as 9 per cent[4] have been reported by others. In six patients (9.6 per cent), there was at least one close relative with proved rheumatoid arthritis or acute rheumatic fever. It is interesting to note that two mothers had lupus erythematosus, one suffered from discoid lupus, the other was afflicted with subacute disseminated lupus.

AGE OF ONSET

General agreement concerning the average age of onset places the peak incidence during the third year, followed by a secondary rise between the eighth and eleventh years of life.[2,4-7,12] In this series, 4.7 years was the average age of onset. In thirty-five patients (56 *per cent*), *symptoms appeared* before the third year. In nineteen of the remaining twenty-seven patients (30 per cent), symptoms appeared first between the eighth and eleventh years The disease began in three patients in the first year of life; in one patient, our earliest, it occurred during the tenth month. This case is not unusual since Sury[4] reported eight patients who developed their disease during the first year. Patients over 12 years of age at onset were not included because they reacted in a pattern typical of the disease in adults

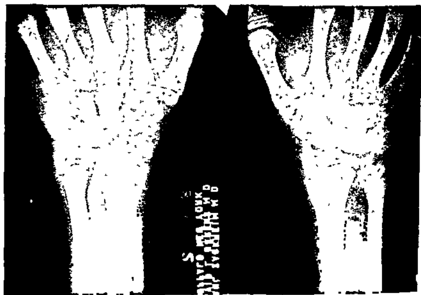


Fig. 3 Roentgenograms of the wrists of an 11 year old boy, illustrating ad vanced *arthritic changes of the right wrist with abnormal carpal development*

PRECIPITATING FACTORS

Since the etiology of rheumatoid arthritis is not known, it is believed that upper respiratory infections should be considered only as a precipitating, rather than the causative factor The frequency of respiratory *disease (especially* due to hemolytic streptococci) just prior to the onset of rheumatoid arthritis is almost as impressive as in rheumatic fever patients. In several reported series, the incidence of prior respiratory infections varied from 45 to 57 per cent[2,6,10] Twenty-two (35.4 per cent) of our patients had a

history of an antecedent upper respiratory infection with hemolytic streptococci cultured from throats in all except three patients.

In our opinion, trauma to a joint is of questionable etiologic significance. In children, a history of injury, especially to knee joints, can be obtained frequently. However, the development of articular symptoms following trauma was observed in only four patients. In two other patients, an interval of several weeks intervened between the "suspected" injury and the occurrence of joint symptoms. One author suggested that trauma was a definite factor in 20 per cent of his patients,[10] but others reported 10 per cent.[3, 6, 7] If trauma is a factor, it is not associated as frequently with the onset of joint symptoms (or with reactivation of the disease) as is a prior respiratory infection. Although trauma may be associated with onset of symptoms, the authors believe it is only coincidental and that it is not the cause of juvenile rheumatoid arthritis. The possible relationship of a hereditary factor in juvenile rheumatoid arthritis, mentioned previously, requires more definite data in order to establish its significance. It is not apparent in this group from available information.



FIG. 4 Roentgenogram of the wrists of a 10 year old boy illustrating abnormal carpal development.

TYPE OF ONSET

The mode of onset was insidious in forty-six (74.2 per cent) of the patients. There was a painless swelling of one or more joints with minimal constitutional reaction. Fever, anorexia, weight loss and anemia were mild but were observed in ten of this group. In the remaining sixteen (25.8 per cent) patients, the onset of the disease was acute, associated with severe and impressive systemic symptoms. This latter group of children developed fever

(up to 105°), severe anemia which required transfusion, cardiac abnormalities, marked weight loss and enlargement of the spleen, lymph nodes and liver. The patients were seriously ill, had a more protracted illness with frequent recurrences and exhibited a poor result eventually.



FIG 5 Roentgenograms of the cervical spine and jaw of an 18 year old girl, illustrating the failure of proper development of the mandible.

CONSTITUTIONAL REACTION

Systemic manifestations were present in twenty-six (42 per cent) of our patients. Twenty-two of these patients represented the more severe group who progressed to stage III or IV disease (A.R.A. classification) at the time of their final evaluation. Moderate anemia, weight loss and fever were transient symptoms in four of the milder patients The systemic findings in all patients are shown in table 1.

TABLE 1

Systemic Manifestations in 26 Patients

Fever	26
Anemia	23
Weight loss	22
Interference with osseous growth	12
Carditis	12
Lymphadenopathy	10
Splenomegaly	9
Hepatomegaly	5
Ocular involvement (scleritis, iridocyclitis)	5
Paralytic ileus	1

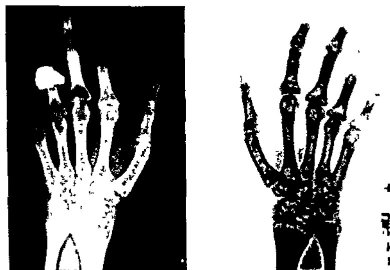


FIG. 6. Roentgenograms of the hands and wrists of the same patient as in figure 5.

Loss of weight was a frequent finding early in the course but usually approached normal when the activity of the disease subsided However, in five patients (including the three fatal cases), weight loss was present con-

tinuously. Failure of normal growth was observed in six patients, of whom two regained normal height when the disease became inactive. Four patients



FIG. 7. Roentgenograms of the pelvis of a 17 year old boy. The progressive changes are illustrated in the succeeding figures. This roentgenogram was taken in 1946 at which time the patient was 6 years of age. The left femoral head and acetabulum demonstrate progressive deformity as a result of the rheumatoid process.

had permanent defects as a result of premature epiphyseal fusion or because of accelerated epiphyseal growth. Since the effect of this disease upon normal bone development and growth represents an interesting and not infrequent finding, these changes will be discussed later in detail.

The occurrence of murmurs, friction rubs and electrocardiographic abnormalities was observed in twelve patients; two patients developed cardiac failure during acute episodes. Postmortem findings of severe pancarditis (similar to rheumatic fever) were present in two of the three fatalities. An autopsy was not obtained in the other patient but cardiac disease was suspected during clinical examination. Six of the twelve patients revealed no evidence of cardiac involvement, but the remaining three patients appeared to be afflicted with valvular disease (two aortic and one mitral stenosis).

INITIAL JOINT INVOLVEMENT

Juvenile rheumatoid arthritis had a predilection initially for involvement of large joints, especially the knee. This is particularly true in the younger patients (up to age 8). In the older patients who are approaching puberty, there is a higher incidence of initial involvement of small peripheral joints, similar to the adult patient. The frequency of joint involvement in our group of sixty-two patients is shown in table 2.

TABLE 2

Joint First Involved		*Later Involvement (during course of disease)*	*Total Involvement (62 patients)*
Knee	36	22	58
Hand	5	32	37
Wrist	7	25	32
Ankle	4	26	30
Elbow	0	20	20
Foot	4	10	14
Hip	3	9	12
Cervical Spine	1	10	11
Shoulder	0	9	9
Sacroiliac	1	4	5
Temporomandibular	1	4	5
	62		

In six patients (9 per cent) only one joint was involved during the course of the disease. Monarticular involvement is unusual in rheumatoid arthritis, but the diagnosis was proved by joint aspiration with negative cultures and synovial biopsy, which demonstrated the typical histologic findings of rheumatoid disease. Monarticular involvement of the knee occurred in four pa-

tinuously. Failure of normal growth was observed in six patients, of whom two regained normal height when the disease became inactive. Four patients



FIG 7 Roentgenograms of the pelvis of a 17 year old boy. The progressive changes are illustrated in the succeeding figures. This roentgenogram was taken in 1946 at which time the patient was 6 years of age The left femoral head and acetabulum demonstrate progressive deformity as a result of the rheumatoid process.

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tients; the hip and ankle joint were affected in the other two patients. Four patients had migratory joint symptoms resembling rheumatic fever before definite, persistent involvement of one or more joints occurred.



Fig 8 Roentgenogram of the hip of the same patient as in figure 7. This roentgenogram was taken in 1947 when the patient was 8



Fig. 9 Roentgenogram of the hip of the same patient as in figure 7. This roentgenogram was taken in 1950 when the patient was 11.

DURATION OF ACTIVITY OF THE DISEASE

Considerable doubt surrounds the duration and course of this disease. Colver[5] reported that the maximum period of activity was seven years (aver-



FIG. 10. This roentgenogram was taken in 1952 when the patient was 13



FIG. 11 This roentgenogram was taken in 1956 when the patient was 17

age five years) and that reactivation did not occur after the disease had been quiescent for eighteen months. However, this has not been the experience of other writers, who have observed continuous activity or recurrences for periods of from eight to more than twenty years.[2, 4, 5, 8, 10] In one series of hospitalized patients, who were more severely afflicted than the average, ten years of continuous activity or recurrences was the rule. One patient had an acute exacerbation of the disease forty years after the first bout of arthritis at age nine.[3] The average duration of activity was sixty-six months in our patients, but recurrences of the disease were observed for periods of as long as twenty years. Forty-one patients experienced only one well defined period of activity. In seventeen patients, the duration of the arthritis was less than two years. This latter group (17 patients) has suffered no exacerbations for at least seven years.

In eighteen patients the disease was active for a period of from 3 to 6 years; in six patients, for 10 years. Twenty-one patients had 62 distinct attacks over a period of 3 to 20 years, an average of three per patient.

TABLE 3

ACTIVITY OF RHEUMATOID ARTHRITIS (62 PATIENTS)

	Number of Patients	*Duration of Activity (Years)*
One period only (41 patients)	17	1-2
	18	3-6
	6	*7-10*

	Patients	*Number of Attacks*	*Duration of Activity (Years)*
Multiple periods of activity (21 patients)	*9*	*2*	
	6	3	3-20
	4	4	
	2	5	

Reactivation of the disease followed upper respiratory infection due to H. streptococci in seven patients and severe trauma (such as in intra-articular fracture or direct trauma to a joint) in three patients. The disease had been inactive in two of the latter group for periods of 10 and 12 years, respectively. Minor traumatic incidents did not result in reactivation of the disease. One patient had a recurrence of the disease following pregnancy after 16 years of quiescence.

DIFFERENTIAL DIAGNOSIS

Juvenile rheumatoid arthritis was confused with other diseases in more than one third of our patients. The greatest difficulty occurred in the differ-

ential diagnosis of rheumatic fever in twelve patients. Four patients who presented a clinical picture of migratory joint symptoms, fever, anemia, cardiomegaly with murmurs, electrocardiographic changes, a good response



FIG. 12 Roentgenogram of the cervical spine and jaw of the same patient as in figure 7. The age at this time was 17. Failure of normal mandibular development and fusion of the posterior articulations of the second and third vertebral bodies are illustrated



FIG 13 Roentgenograms of the knees of a 10 year old girl in 1955 This roentgenogram was taken when the patient was 7.



FIG 14 Roentgenogram of the knees of the same patient as in figure 13 This roentgenogram was taken three years later

to salicylates and bed rest, were observed for a period of from several months to five years (in one patient), before a final diagnosis could be made. Eventually, the diagnosis was determined by persistent localized joint signs, clinically and radiographically. The clinical picture of rheumatoid arthritis became rapidly apparent in the other eight patients. However, six patients of this latter group subsequently developed carditis (2 of 3 fatal cases were confirmed at autopsy), the three living patients have persistent cardiac abnormalities (two, aortic stenosis and one, mitral stenosis).

In six patients with monarticular involvement, it was possible to exclude a specific infectious arthritis (especially tuberculosis), by means of joint aspiration and culture, tuberculin test and biopsy of the synovia in three patients. Leukemia was considered presumptively in three patients because of splenomegaly, lymphadenopathy and a marked leukocytosis with immature granulocytes. Osteomyelitis was suspected in two patients; they developed subsequently typical joint signs of rheumatoid arthritis.

TREATMENT

Treatment of juvenile rheumatoid arthritis does not differ from that of the adult form; the program employs the same fundamental measures of bed rest, physical medicine, supportive therapy for general health, orthopedic procedures to prevent or correct deformities, and, in some patients, the administration of gold salt injections or hormones. The most effective treatment in our experience has been prolonged bed rest in combination with adequate physical therapy, when this program can be carried out intelligently in the pleasant, reassuring atmosphere of the home. Complete bed rest is continued until all evidence of joint inflammation has subsided.

The evaluation of drugs (chrysotherapy or hormones) is difficult because the disease is often self limited and subject to remissions or recurrences. Chrysotherapy was administered to thirty-five patients (weekly injections of 10-20 mg until a total of 600-900 mg was given), twenty-three (65.7 per cent) patients improved during the period of gold treatment. Gold therapy was discontinued in seven patients because of a dermatitis and in three other patients because of "suspected" systemic reactions.

In twenty patients, corticotrophin or adrenal cortical steroid therapy was given. All patients had immediate relief of constitutional and joint symptoms and suffered no adverse side effects other than the typical "moon face," acne-form eruptions or abnormal weight gain. No reactions were encountered which justified discontinuance of hormone therapy. There can be no question but that hormone therapy diminished the severity of the disease in every patient. Several patients who were almost complete invalids (bed or wheelchair patients) had marked improvement of joint function, weight gain and growth. The only discouraging factor was the radiographic demon

stration of progressive arthritic changes in five patients, despite marked clinical improvement. However, it is our firm belief that hormones are of benefit in juvenile rheumatoid patients and should be administered to all



FIG. 15 Roentgenogram of the cervical spine of the same patient as in figure 13 Patient was 7 years of age

children with severe joint involvement and constitutional symptoms. Hormone therapy is not given to patients with mild juvenile rheumatoid arthritis as they respond well to conservative therapy and chrysotherapy.



FIG. 16 Roentgenogram of the cervical spine of the same patient as in figure 13 and 15. This roentgenogram was taken when the patient was 12, five years after figure 15. Fusion of the second to the fifth vertebrae and subluxation at cervical 5 and cervical 6 are illustrated.

PROGNOSIS AND RESULTS

The prognosis of juvenile rheumatoid arthritis in this group is not as grim as the original description by Still[1] or the recent report by Barkin[2] would indicate. An explanation for the "poor" results is that their series included a high incidence of severe cases requiring hospital care and excluded the "mild" patients encountered in office or out-patient practice. The final result of Barkin's[2] 51 patients are as follows:

(1) 11 dead (20 per cent)
(2) 21 functional recovery (41 per cent)
(3) 19 severely handicapped (39 per cent)

When these figures are compared with other results,[3, 4, 7, 8, 10] it is apparent that they represent an abnormally severe group. Our results confirm a more optimistic prognosis. At a recent follow-up examination they were tabulated both as to stage of the disease and functional capacity, according to the American Rheumatism Association classification:

Disease inactive	45 patients—72.5 per cent	Total 62 patients
Disease active	14 patients—22.5 per cent	
Died of disease	3 patients—4.8 per cent	

TABLE 4
STAGE OF DISEASE AT MOST RECENT EXAMINATION

	Number of Patients	*Total Patients*	*Total Patients* (percentage)	
STAGE I				
Inactive	16	17	27.4	Good Recovery
Active	1			
STAGE II				
Inactive	15	23	37.1	
Active	8			
		40	64.5	
STAGE III				
Inactive	11	15	21.2	Poor Recovery
Active	4			
STAGE IV				
Inactive	3	4	6.5	
Active	1			
Died	3	3	4.8	
		22	35.5	



FIG 17 Roentgenogram of the pelvis of the same patient as in figure 13 This roentgenogram was taken in 1950, patient was 7



FIG. 18. Roentgenogram of the pelvis taken five years after that illustrated in figure 17 Rheumatoid changes are apparent with little interference of bone development

TABLE 5

FUNCTIONAL CAPACITY AT MOST RECENT EXAMINATION

	Number of Patients	Total Patients	Total Patients (percentage)	
CLASS I				
Inactive	23	26	41 9	Normal Functional Capacity
Active	3			
CLASS II				
Inactive	14	22	35 5	
Active	8			
		48	77 4	
CLASS III				
Inactive	6	8	12 9	Limited Functional Capacity
Active	2			
CLASS IV				
Inactive	2	3	4 8	
Active	1			
Died	3	3	4 8	
		14	22 5	



FIG 19 Roentgenogram of the pelvis of a 14 year old girl afflicted with rheumatoid arthritis at the age of 7 There is fusion of both knees Extensive rheumatoid changes are illustrated.

FACTORS WHICH AFFECT PROGNOSIS

The prognosis of juvenile rheumatoid arthritis was unfavorably influenced in these patients by a prolonged duration of activity and by an



FIG. 20. Roentgenograms of the lower legs of the same patient as in figure 19. There is fusion of both knees, ankles and feet and premature fusion of the tibial epiphysis and overgrowth of the fibula with considerable bowing.

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Active	1	3	4 8	
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		14	22 5	



FIG 19 Roentgenogram of the pelvis of a 14 year old girl afflicted with rheumatoid arthritis at the age of 7 There is fusion of both knees Extensive rheumatoid changes are illustrated.

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FIG. 20 Roentgenograms of the lower legs of the same patient as in figure 19 There is fusion of both knees ankles and feet and premature fusion of the tibial epiphyses and overgrowth of the fibula with considerable bowing

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FUNCTIONAL CAPACITY AT MOST RECENT EXAMINATION

	Number of Patients	*Total Patients*	*Total Patients* (percentage)	
CLASS I				
Inactive	23			
Active	3	26	41 9	
CLASS II				Normal Functional Capacity
Inactive	14			
Active	8	22	35 5	
		48	77 4	
CLASS III				
Inactive	6			
Active	2	8	12 9	
CLASS IV				Limited Functional Capacity
Inactive	2			
Active	1	3	4 8	
Died	3	3	4.8	
		14	22 5	



FIG. 19 Roentgenogram of the pelvis of a 14 year old girl afflicted with rheumatoid arthritis at the age of 7 There is fusion of both knees Extensive rheumatoid changes are illustrated.

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Active	1			
Died	3	3	4 8	
		14	22 5	



FIG 19 Roentgenogram of the pelvis of a 14 year old girl afflicted with rheumatoid arthritis at the age of 7 There is fusion of both knees Extensive rheumatoid changes are illustrated.

FACTORS WHICH AFFECT PROGNOSIS

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FIG. 20 Roentgenograms of the lower legs of the same patient as in figure 19. There is fusion of both knees, ankles and feet and premature fusion of the tibial epiphysis and overgrowth of the fibula with considerable bowing.

acute onset with severe constitutional reaction to the disease. The three patients who died and ten other patients who have the most severe joint damage were in the group of sixteen patients with an acute onset. The remaining nine patients with irreparable joint deformities were those with prolonged activity and frequent acute exacerbations There was no apparent relation of the ultimate prognosis to the age at onset, the sex of the patient, or to the specific joints affected in our patients.

CAUSE OF DEATH

Three patients (4 8 per cent), each severely crippled (stage IV, class IV) have died In addition to severe rheumatoid deformities, pancarditis and amyloidosis, one patient had pulmonary tuberculosis and the second patient had staphylococcus septicemia with multiple abscesses. The third patient, who died in another hospital of an acute exsanguinating uterine hemorrhage (at her menarche), was not examined post mortem but was believed to have amyloidosis and carditis at previous clinical examinations. The average duration of disease from onset to death was 9.3 years (7, 9 and 12 years, respectively)

INTERFERENCE WITH NORMAL OSSEOUS GROWTH

In addition to retarded general development and loss of weight, which was temporary in most patients, complex and bizarre effects were noted on the normal pattern of osseous growth. These changes include premature or retarded appearance of epiphyses, premature fusion of epiphyses with failure of normal bone growth, stimulation of epiphyses with excessive growth, periosteal growth along the shaft of the phalanges, and abnormalities resulting from various combinations of these factors and the arthritic process

Osseous growth disturbances were observed in twelve patients (including the three fatal cases). The regions most frequently involved were as follows:

(1) Cervical vertebrae	8
(2) Mandibles	7
(3) Hands and Wrists	7
(4) Hips	5
(5) Disproportionate growth in one extremity	4
A. Forearm	4
B Leg	3

Abnormalities of osseous development are frequent in the experiences of others [2, 8, 14-16] and were reported in 22 of 56 patients (30 per cent).[8] The most frequent disturbances were brachygnathia (maldevelopment of the mandible, so-called "bird-jaw"), brachydactylia (short, stubby fingers) and



FIG. 21. Roentgenogram of the left forearm of the same patient as in figure 19. Premature fusion of one epiphysis with excessive growth of the other is apparent.

fusion of the cervical vertebrae. The appearance of "dwarfism" was not uncommon in patients who reached maturity.[8] The most comprehensive review of this subject in 119 juvenile rheumatoid patients was published recently.[11]



Fig 22 Roentgenogram of the right forearm of the same patient as in figure 19 Extensive arthritic changes are illustrated

We have not observed the high percentage (80 per cent) of spondylitis reported by Barkin[17]; only 25 per cent of our juvenile patients have evidence of spinal involvement on clinical and radiographic examination. Osseous abnormalities have occurred more often in the older age group (6-12 years) and also in patients with persistent activity of rheumatoid disease for man

years. Figures 1-27 demonstrate some of the typical skeletal disturbances of rheumatoid arthritis in children.



FIG. 23 Roentgenogram of the hands of a 3 year old boy suffering from rheumatoid arthritis.



FIG. 24 Roentgenogram of the hands of the same patient as in figure 23. This roentgenogram was taken five months later and demonstrates periosteal bone formation

SUMMARY

Juvenile rheumatoid arthritis is a chronic joint disease of children, associated with systemic manifestations in 40 per cent. The peak incidence occurs during the first three years of life, with a secondary rise between the eighth and eleventh years. Females were affected more frequently than males (2.1).

The important precipitating cause of the disease is a preceding respiratory infection (when associated with the hemolytic streptococcus) Heredity may also be a potent contributing factor but more data are required to prove its role at the present time.

The course of juvenile rheumatoid arthritis is variable. The disease is often mild in severity with a duration of less than two years in one fourth of the patients. However, the joint and systemic involvement are severe in another twenty-five per cent of the patients in whom the disease process may continue to be active for twenty years or more, with frequent recurrences.

The average duration of activity was sixty-six months after onset in this group of sixty-two patients. The ultimate prognosis of the disease was determined by the type of onset, by the duration of activity and the number of recurrences. The sixteen patients (25 per cent) who had an acute onset with typical so-called "Still's disease" suffered the poorest result.

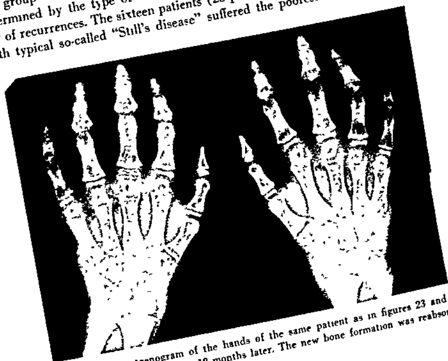


Fig 25 Roentgenogram of the hands of the same patient as in figures 23 and 24 This roentgenogram was taken 18 months later. The new bone formation was reabsorbed at this time



FIG. 26. Roentgenograms of the elbow of the same patient as in figure 23. Marked destructive changes are illustrated.

Abnormal osseous development resulted from disturbance of the arthritic process on the growing epiphyses in approximately 20 per cent. Unusual deformities of the skeletal system (so-called "bird-jaw," fusion of cervical vertebrae resulting in a short neck, or unequal growth of bones in the extremities) are characteristic of this group of patients.

In our experience, there is no valid reason to consider "Still's disease" as a definite entity. All gradations of the disease are encountered in the same child during separate attacks and there is no basic pathologic difference from rheumatoid arthritis in the adult patient.

The prognosis for ultimate recovery is good; forty-eight patients (77.4 per cent) have maintained normal function of their joints after an observation period of from seven to twenty years. Only three patients (4.8 per cent) have died; eleven (17 per cent) of the group have severe joint disability.

Treatment of juvenile rheumatoid arthritis is difficult to evaluate because of the variable nature of the disease. The same procedures of established value are employed as in the adult form of rheumatoid arthritis. Prolonged bed rest combined with chrysotherapy and adequate physical therapy produced the best results when it was possible to carry out such a program in the reassuring atmosphere of an intelligent and sympathetic home. The judicious use of hormones reduced the morbidity of the disease in severely

involved patients. When hormone therapy was carefully withdrawn and eventually eliminated, no exacerbations of the disease process were encountered



Fig 27 Roentgenogram of the chest of the same patient as in figure 23 Enlargement of the heart is illustrated

References

1. Still, G. F.: On a form of chronic joint disease in children. Medicochirurgical Trans. *80* 47, 1897.
2. Barkin, R. E.: The clinical course of juvenile rheumatoid arthritis. Bull Rheum Dis. 3: 37, 1952.
3. Bille, B.: Kronisk polyartrit hos barn och dess guldenhandling. Nord Med 37 307, 1948.
4. Sury, B.: Rheumatoid Arthritis in Children—A Clinical Study. Münksgaard, 1952.
5. Colver, T.: The prognosis in rheumatoid arthritis in childhood. Arch. Dis. Childhood *12*. 253, 1937.
6. Coss, J. A. and Boots, R. H. Juvenile rheumatoid arthritis, study of fifty-six cases with a note on skeletal changes. J. Pediat. 29 143, 1946.
7. Edstrom, G. Rheumatoid arthritis in children. Acta pediat. *34* 339, 1947.
8. Fyfe, W. M. Rheumatoid arthritis in childhood. Glasgow M. J. *36*: 102, 1955.
9. Holzmüller, G.: Beitrag zur Frage der Pathogenese und Therapie der primär chronischen Gelenkerkrankungen im Kindesalter. Ztschr. f. Rheumaforsch 5 57, 1942.
10. Pickard, N.: Rheumatoid arthritis in children: a clinical study. Arch. Int. Med *80* 771, 1947.
11. Wissler, H. Der Rheumatismus im Kindesalter. Teil 2. Die chronische Polyarthritis des Kindes. Dresden und Leipzig, 1942 (p. 152).
12. Bunim, J. J., Kuttner, A. G. Baldwin, J. S. and McEwen, C. Cortisone and cortico-tropin in rheumatic fever and juvenile rheumatoid arthritis. J.A.M.A. *150* 1273, 1952.
13. Lockie, L.M. and Norcross, B. M. Juvenile rheumatoid arthritis. Pediatrics *2* 694, 1948.
14. Ansell, B. M. and Bywaters, E. G. L. Growth in Still's disease. Ann. Rheum. Dis. *15* 295, 1956.
15. Engel, M. B., Richmond, J. B. and Brodie, A. G. Mandibular growth disturbance in rheumatoid arthritis of childhood. Am. J. Dis. Child. 78 728, 1949.
16. Middlemiss, J. H. Juvenile rheumatoid arthritis (Still's disease). Proc. Roy. Soc. Med. *44* 805, 1951.
17. Barkin, R. E., Stillman, J. S. and Potter, T. A. The spondylitis of juvenile rheumatoid arthritis. New England J. Med. 253 1107, 1955.

Felty's Syndrome

by W. K. Ishmael

SINCE IT WAS FIRST REPORTED IN 1924, the triad of rheumatoid arthritis associated with splenomegaly and leukopenia in adults has been designated Felty's[1] syndrome. Chauffard and Ramond[2] in 1896 were the first to report gross enlargement of the spleen in rheumatoid arthritis, while this occurrence in children was reported a year later by Still.[3] Although these reports have served to point out important systemic manifestations associated with rheumotoid arthritis, the eponyms "Felty's syndrome" in adults and "Still's disease" in children lack the clarity of descriptive nomenclature The 1956 Rheumatism Review[4] does not give preference to the term Felty's syndrome, and the synonym Still's disease has been omitted from the section on juvenile rheumatoid arthritis

American rheumatologists for the past ten years are almost unanimous[5] in believing that Felty's syndrome is not a separate disease entity; rather, they consider the patient to have rheumatoid arthritis manifesting an unusual reticuloendothelial response. Indeed, the term probably would have been entirely discarded by now were it not for the fact that very gradually the syndrome has become therapeutically distinct, in that splenectomy has proved to be of at least some value in only this type of arthritis.

Lockie et al[6] in 1942 stated that the eponym Felty's syndrome in its broadest sense should be retained, for "by synthesizing the different findings it serves as a convenience in discussion of differential diagnosis." They pleaded, however, that Felty's syndrome not be made a nosologic waste basket through a loose and compromising attitude toward the criteria required for such a diagnosis. They further specified that "the patient should be an adult with chronic rheumatoid arthritis, with splenomegaly and neutrophilic leukopenia of a definite degree."

If one regards the Felty syndrome purely from the nosologic standpoint, then undoubtedly these three criteria should be rigidly adhered to. If, however, one approaches the patient from the standpoint of treatment, it may be expedient to modify certain aspects of the criteria. First, it is well to review Felty's original report

CLINICAL FEATURES

The observations described by Felty were concerned with three male and two female patients, aged 45 to 65 years. The clinical features common to these patients were.

1. Chronic arthritis characterized by acute exacerbations, resulting in deformities indistinguishable from those characteristic of rheumatoid arthritis.

2. General debility in some, resulting in severe cachexia

3. Characteristically nontender splenomegaly, the spleen enlarged to the level of the umbilicus in three of the patients

4. Leukopenia manifested by reduction in polymorphonuclear leukocytes The anemia characteristic of rheumatoid arthritis was also present The platelet count, bleeding time, coagulation time, and erythrocyte fragility tests were reported to be normal in this group of patients.

General pallor, accompanied by light to dark brown pigmentation, more prominent over the exposed skin surfaces, were observed

INCIDENCE

Since Felty's original report, approximately seventy papers have been published relative to this syndrome All are agreed on at least one item: it is of relatively rare occurrence Reports on the incidence of splenomegaly in rheumatoid arthritis vary to an amazing degree, averaging from one per cent[7] to 21 per cent.[8] In our clinics splenomegaly in patients with rheumatoid disease is limited almost to children, and when it occurs in adults, systemic lupus erythematosus is usually present The reported incidence of leukopenia understandably varies due to variance of accepted normals However, if values below 2000 are considered as neutropenia, the incidence of less than .5 per cent reported by Collins[9] is probably a reasonable figure. To encounter an adult patient with rheumatoid arthritis manifesting both true neutropenia and unquestioned splenomegaly would obviously be a rare observation Three such patients have been recognized in our clinics in the past fifteen years A review of the literature reveals that there are almost as many papers written on the subject of Felty's syndrome as there have been patients reported.

THEORETICAL CONSIDERATIONS

We do not have critical information to correlate the basic aspects of the interrelationships between the reticuloendothelial and the ground substance changes present in various of the collagen diseases. Hence, any conclusions or deductions reached at this time regarding their association would of necessity be theoretical There does appear to be a fundamental reticuloendothelial lability in the collagen disorders The marked leukocytosis that frequently occurs in rheumatoid arthritis in children has probably the same cause-effect relationships as the leukopenia occurring in adult patients in the type of arthritis under discussion Collagen reticuloendothelial interreactions are not limited to rheumatoid arthritis. Indeed, the coexistence of leukopenia, splenomegaly, pyrexia, severe wasting, and malaise, along with

articular involvement, is fundamentally more characteristic of systemic lupus erythematosus[10] (S.L.E) than rheumatoid arthritis.

Fundenberg and Wintrobe[11] in 1955 reported a classical case of scleroderma with enlarged spleen and symptomatic hemolytic anemia. Previously, these findings had been reported in patients with polyarteritis nodosa by Dameshek and Rosenthal[12] in 1951 and by Lovshin[13] in 1952. Laszlo et al.[14] reported a patient with thrombotic thrombocytopenic purpura and disseminated lupus erythematosus associated with splenomegaly and primary anemia with fatal outcome. Not only have splenomegaly and cytopenia been reported in all of the collagen disorders, but their association with arthritis has also been reported in cirrhosis of the liver, pernicious anemia, amyloid disease, leukemia, lymphadenoma, agranulocytosis, hemolytic anemia, acute and chronic infections, and septicemias.[15] If the patient with Felty's syndrome is considered from the therapeutic standpoint, this latter group of disorders should be carefully excluded, since they are therapeutically and prognostically quite different. It is possible that some of the discrepancies in the literature on the results of treatment are based on the failure to exclude some of the above disorders.

As far back as 1889, Bauer[16] stated that neutropenia could be the result of overactivity of the spleen. Frank[17] in 1916 pointed out that neutropenia may occur with splenomegaly of diverse etiology. In the same year, Kazelson[18] first reported a rise of the platelet count following removal of the spleen in thrombocytopenia Since then, splenectomy for thrombocytopenia steadily has become more firmly established, as experience has proved its value, substantiating the cause and effect of hypersplenism and thrombocytopenia. Comparatively speaking, the direct casual relationship of an enlarged spleen and neutropenia is still somewhat in the theoretical stage, however. Reissmann[19] in 1938 and Wiseman and Doan[20] in 1939 described the "primary" form of splenic neutropenia and pointed out that splenectomy might be curative.

In recent years there has been a revival of interest in overactivity of the spleen as a cause of neutropenia, although uncertainty still exists regarding not only the cause of the hypersplenism but also the mechanism by which the neutropenia occurs. Doan and his associates[20-22] are convinced that the cause lies in excessive sequestration and phagocytosis by the spleen, whereas Dameshek and his co-workers[10, 23] believe that the spleen exerts an inhibitory effect on the production of neutrophiles by the marrow. Other factors, especially where there is an associated collagen type of arthritis, could be concerned. Hutchinson and Alexander[24] in 1954 demonstrated that no single mechanism is invariably concerned in splenic neutropenia and that either the mechanism described by Doan, or that described by Dameshek, may be the cause in individual cases, thus permitting recognition of at least two forms

of the disease Hutchinson and Alexander state that splenic neutropenia associated with arthritis is possibly more common than has been generally suspected They believe that some cases of so-called primary splenic neutropenia are merely examples of an exaggerated form of Felty's syndrome. Reporting such a case, in which remission followed splenectomy, they concluded, "Felty's syndrome may be a fairly common cause of what has been regarded as primary splenic anemia." In addition to their own patient, they report twenty-one cases from the literature in which splenectomy for neutropenia was effective. It is interesting to note that ten of these twenty-one cases reported had an associated arthritis.

Since Felty's original report, many significant papers have been published on this subject,[6, 9, 13, 19, 20, 22, 48, 50] over forty of these papers on the value of splenectomy.[3, 6, 9, 10, 12, 14, 15, 18, 27, 30-40, 42, 47, 50-60] Review of these publications reveals a paucity of information regarding the etiology of the syndrome or its nosologic significance One is impressed, nonetheless, with the reported value of splenectomy in this syndrome, however lacking its modus operandi. In 1953 Steinberg[3] presented data on the subject of splenectomy in Felty's syndrome. In this communication he offers a new concept toward the manner in which splenectomy affects both the cytology and collagen reaction in the patient with Felty's syndrome.

In addition to the concepts of Dameshek[19, 23] (splenic inhibitory effect on marrow) and Wiseman and Doan[20-22] (plasmocytosis with excessive phagocytosis of the granulocytes), Steinberg[40] had previously noted that there was a hyperplastic marrow in Felty's syndrome occurring with leukopenia and pancytopenia In view of the fact that the cell depression was noted only in the peripheral blood, he concludes that the spleen acted in some way as a barrier between the overactive bone marrow and the cytopenia in the peripheral blood. Hirschboeck[41] noted in one case a white blood count of 11,700 in the splenic artery, in contrast with a white blood count of 2,600 in the splenic vein These data stimulated Steinberg to investigate further the modus operandi of splenectomy in cytopenia.

Review of pertinent data regarding pituitary-splenic axis revealed that Smith[51] in 1930 was the first to report that atrophy of the spleen (and other target or endocrine glands) was a sequel to hypophysectomy in the rat. Perla[52] in 1936 reported the following

1. Removal of the pituitary in an adult rat resulted in progressive atrophy of the spleen

2. Hypophysectomy completely inhibited regeneration of splenic tissue after partial splenectomy.

3 Daily administration of anterior pituitary emulsion to rats over a ten day period resulted in hypertrophy of the spleen to twice normal size.

It was further shown that alkaline extracts of anterior pituitary caused this enlargement of the spleen, whereas acid extracts (containing thyrotropic and adenotropic factors) had no such effects on the spleen.

Friedgood[63] in 1936 also demonstrated that injections of an alkaline extract of the anterior pituitary in adult male and female guinea pigs produced splenomegaly.

Waugh[64] in 1932 reported autopsy findings in a patient in whom the spleen had been removed four years previously, who demonstrated that the anterior lobe of the pituitary gland was twice normal size.

Steinberg then presented six case histories of patients with rheumatoid arthritis, leukopenia and splenomegaly in whom three had had splenectomy and three had been given glucocorticoids or corticotropin. Of the three who had had splenectomy, all had remission of the arthritis and cytologic phenomena. Two of the patients given glucocorticoids or corticotropin developed remissions with prompt relapse following withdrawal of the drug. The sixth patient was presented to demonstrate enlargement of the spleen with leukopenia eleven months following withdrawal of glucocorticoids. These findings were not present prior to this therapy.

Steinberg concluded in this presentation, "Cortisone and corticotropin result in temporary improvement in the blood picture and diminution of the spleen in cases of rheumatoid arthritis associated with splenomegaly and leukopenia. There is evidence to indicate that this medication does not prevent the onset of the syndrome and does not result in permanent reversal of the syndrome. Splenectomy appears to be the treatment of choice in these cases. Evidence is presented to suggest that the removal of the spleen results in hypertrophy of the anterior lobe of the pituitary. If this be true, then the procedure actually sets in motion a constant and increased supply of corticotropin in the individuals. A new method of approach to the problem of rheumatoid arthritis therapy is suggested in this paper."

The relationship of the anterior pituitary gland to rheumatoid arthritis is far from settled at this time. At least, gross change has not been consistently demonstrable in patients with rheumatoid arthritis. Certainly one should keep an open mind toward future developments in the spleno-pituitary-collagen disease axis.

Correlation of the diverse publications on splenectomy in patients with the manifestations of hypersplenism would indicate that leukopenia, thrombocytopenia or primary "splenic" anemia, or any combination of these cytopenias, may occur in a given patient, with or without splenomegaly or arthritis. The majority of these publications over the last ten years indicate a favorable response of at least the blood elements to splenectomy.

The arthritic syndrome encountered in the reported cases of Felty's

syndrome was by and large indistinguishable from "typical" adult rheumatoid arthritis. As mentioned above, however, splenomegaly, neutropenia, pyrexia, wasting and malaise are fundamentally more characteristic of S.L.E. than rheumatoid arthritis. In recent years, widespread utilization of the lupus cell test[13] devised by Hargrave, and autopsy studies on patients with rheumatoid arthritis who have died following prolonged glucocorticoid therapy[14] have demonstrated that many patients previously considered to have rheumatoid arthritis actually have systemic lupus erythematosus. Hence, it would appear that from the therapeutic standpoint, one should modify the diagnostic criteria outlined by Felty and emphasized by Lockie et al. In addition to leukopenia, one should also include as a criterion of diagnosis thrombocytopenia or primary "splenic" anemia, or any combination of these three. In addition to rheumatoid arthritis, one should include at least systemic lupus erythematosus and possibly thrombotic thrombocytopenic purpura, polyarteritis, dermatomyositis, and systemic scleroderma as one of the criteria of Felty's syndrome.

A recent important publication by Dameshek and Reeves[10] has shed considerable light on this problem. They report that "the association of auto-immune hemolytic anemia and of thrombocytopenic purpura with disseminated lupus is well known." It should be said parenthetically that leukophilic leukopenia was noted to be associated with S.L.E. even before the other cytopenias. These authors further state, "In fact, it has become increasingly apparent that when either of the first two conditions is present, one should think of disseminated lupus as a possible underlying disturbance even in the absence of such objective phenomena as the characteristic rash or the joint manifestations." They add, "We have used the (L.E.) test as a routine measure in every case presenting auto-immune hemolytic anemia, 'idiopathic' thrombocytopenic purpura, idopathic neutropenia, splenomegaly of undetermined origin, or the like."

These authors, in this communication, present three cases, two of autoimmune hemolytic anemia and one of idiopathic thrombocytopenic purpura, all with joint manifestations. Two of the three had splenomegaly and hepatomegaly, while in the third patient these organs were not palpable. Repeated lupus cell preparations were reported negative in all three of the patients on initial examinations. Splenectomy was performed on all of the patients, and it is of interest to note that the L.E. cell test became positive in all within nine to twenty weeks following the splenectomy. The typical vascular and perivascular "onion skin" lesions were present in all three of the spleens examined postsurgically, indicating that S.L.E. was present in all three patients in spite of negative L.E. preps prior to surgery.

Whereas Dameshek and Reeves indicated that an exacerbation of the S.L.E. had been provoked by the splenectomy, it is of interest to note that

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in all three patients, the splenogenic elements of the blood disturbance h returned to normal, and the rheumatic complaints had completely subside four and one-half years, three years, and four years, respectively, followin splenectomy. Two of the patients were being maintained without the use o glucocorticoids which prior to surgery could not have been withdrawn without provoking severe exacerbations of both the disturbed blood elements and the articular phenomena

TREATMENT

Whereas the use of aspirin, physical therapy, and rest is frequently rewarding in the treatment of uncomplicated rheumatoid arthritis, the coexistence of splenomegaly and cytopenia presents a therapeutically unique problem which requires critical diagnosis and definitive management. First, the type of collagen or articular disorder must be critically identified and evaluated. Regardless of how typical a rheumatoid may appear, S.L.E. has at least a three percent chance of being present.[67] If the patient has been receiving cortisone or prednisone compounds, and if withdrawal of this medication provokes chills, fever, chest pain, and angiitis with severe exacerbation of the musculoskeletal complaints, and particularly if symptoms and findings referable to the central nervous system develop, S.L.E. or P.A.N. is likely present. Secondly, the presence of an enlarged spleen, regardless of the cause, if associated with hyperplastic bone marrow, raises the question of splenectomy. Should severe neutropenia, especially if severe infections have occurred, chronic thrombocytopenia, "splenic" anemia, or any combination of these three cytopenias exist, with or without enlargement of the spleen, splenectomy must be considered and the patient evaluated for this procedure.

Whether or not, or when, splenectomy should be performed is a difficult decision and may require the aid of a hematologist and a surgeon. First, leukemia, lymphosarcomas, infections, and the other noncollagen conditions mentioned above must be specifically excluded. Some confusion exists regarding the status of bone marrow Most authors agree that splenectomy is indicated only if a hyperplastic marrow exists. Salzer, Ransoff, and Blatt,[65] Alt,[69] and Smith and McCabe,[36] however, report satisfactory results following splenectomy in the presence of a hypoplastic marrow. Undoubtedly, the degree of severity of the involvement of the blood elements would influence one's opinion. It would seem, however, that if clinical deterioration is to be avoided, one should not delay splenectomy too long.

Unfortunately, most patients reported with Felty's syndrome have a relatively advanced degree of arthritis, most of them being in stage III to IV, class III to IV. This fact has made evaluation of the response of the arthritis following splenectomy quite difficult. Certainly, if splenectomy

offers any hope of altering the course of the collagen disease, it should be performed before irreversible changes have occurred.

The wisdom of performing splenectomy in patients with S.L.E. associated with hypersplenism is still in doubt. Undoubtedly, additional light will be shed on this subject by the follow-up on patients such as reported by Dameshek.[10] In the light of our present knowledge, it would appear that if the hypersplenism present offers a threat to the life of a patient with S.L.E., splenectomy is not contraindicated, everything else being equal.

The use of glucocorticoids has been recommended in both the collagen diseases and hypersplenism[5, 24, 41] and they exert at least temporary benefit in the majority of patients with either of these disorders. Their prolonged use, however, is not always prudent, but at least they frequently offer temporary life-saving remissions which may afford sufficient respite, during which time splenectomy may be considered. Whole blood transfusions are usually needed due to the defects produced by the cytopenias. Should the lupus cell preparation reveal typical Hargrave's cells, or even evidence of marked desoxyribonucleic acid depolymerization, transfusions must be administered with care as untoward reactions are prone to occur. Gold, phenylbutazone, aminopyrine, the sulfa drugs, and all substances which may lower the white count are contraindicated in Felty's syndrome, according to Brugsch[70] in his recent text. Chloroquine or hydroxychloroquine merit consideration as a therapeutic aid, particularly if the lupus cell preparation is positive or "false positive." (Inclusion bodies still retain some strands of chromatin material.[71]) The antimicrobial agents may be needed in Felty's syndrome, especially if the neutropenia is sufficiently severe to allow overwhelming infections.

The severity of systemic involvement usually demands unusual protection from stress, especially loss of sleep, exposure, pain, and atrophy of disuse. Particular care should be taken to avoid exposure to sunlight if there is a question of S.L.E. The nutritional status of most patients with Felty's syndrome usually leaves much to be desired. In addition to a high protein, mineral and vitamin diet, supplemental feedings of these substances may be indicated.

SUMMARY

1. The triad of adult rheumatoid arthritis, splenomegaly, and neutrophilic neutropenia, known as "Felty's syndrome," occurs but rarely. Its nosologic significance is unknown at this time, but from the standpoint of treatment, this syndrome is a separate entity.

2. It is proposed that if Felty's syndrome is a therapeutically distinct disease, its concept should be broadened to include thrombocytopenic purpura

and primary "splenic" anemia, as well as neutropenia or any combinati of these three cytopenias, whether or not the spleen is palpably enlarged.

3. Likewise, there is good evidence to show that systemic lupus erythematosus should be included as one of the diagnostic criteria of Felty's syndrome. There is also a possibility that thrombotic thrombocytopenic purpura, systemic scleroderma, polyarteritis nodosa, and dermatomyositis should also be considered as one of the diagnostic criteria

4. Leukemia, lymphosarcoma, infections, cirrhosis, amyloid disease, and agranulocytosis should always be excluded in patients with a collagen disorder and pancytopenia, as they are known to produce a similar picture.

5 Splenectomy is the treatment of choice in Felty's syndrome unless conditions exist in the individual concerned which contraindicate this surgical procedure There is evidence to show that this definitive treatment should not be unduly delayed.

6 Whole blood transfusions, chloroquine and hydroxychloroquine, antimicrobial agents, and the glucocorticoids have a place in the management of certain situations encountered in this disease

7 It is hoped that consideration of Felty's syndrome will not be discarded until the causal interrelationship of disorders of the reticuloendothelial and ground substance systems has been resolved.

References

1 Felty, A R Chronic arthritis in the adult associated with splenomegaly and leukopenia Bull Johns Hopkins Hosp 35 16, 1924
2 Chauffard, A and Ramond, F. Rev med 16 345, 1897.
3 Still, G F Trans Roy Med Chir Soc. 80. 47, 1897
4 Rheumatism and arthritis review of American and English literature of recent years (Eleventh Rheumatism Review) Part 1. Robinson, W. D., Bunin, J J., Clark, W S, Crain, D C, Engleman, E P., Graham, D C., Montgomery, M M., Norcross, B M, Ragan, C., Ropes, Marian, Rosenberg, E F., and Smyth, C J Ann Int Med 45 5, 1956
5 Steinberg, C L. Splenectomy in rheumatoid arthritis Ann Int. Med 38 4, 1953
6 Lockie, L M, Sanes, S, and Vaughan, S L. Chronic arthritis, associated with neutrophilic leukopenia, splenomegaly and hepatomegaly ("Felty's Syndrome"). Am J Clin Path 12 372-379, 1942
7 Hench, P S J A M A 101 2078, 1933
8 Hench, P S, et al Problem of rheumatism and arthritis, review of American and English Literature for 1935 Ann Int Med 10 754-909, 1936
9 Collins, D H Neutrophil leukopenia with enlargement of liver and spleen in rheumatoid arthritis, with a note on the leukocytic blood picture in chronic rheumatism Rep Chron Rheum Dis 3 49-58, 1937.
10 Dameshek, W., and Reeves, W H. Exacerbation of lupus erythematosus following splenectomy in "idiopathic" thrombocytopenic purpura and autoimmune hemolytic anemia Am J Med 31 560-566, 1956

11. Fundenberg, H., and Wintrobe, M. M., Scleroderma with symptomatic hemolytic anemia a case report Ann Int Med 43 201 205, 1955
12. Dameshek, W, and Rosenthal, M. C. Treatment of acquired hemolytic anemia, with a note on the relationship of periarteritis nodosa to hemolytic anemia M. Clin North America 35 1423, 1951.
13. Lovshin, L. L.: Association of acquired hemolytic anemia with periarteritis nodosa, case report. Cleveland Clin. Quart 19 28, 1952
14. Laszlo, M H, Alvarez, A., Feldman, Frederick The association of thrombotic thrombocytopenic purpura and disseminated lupus erythematosus report of a case Ann. Int Med 42 1308 1320, 1955
15. Talkov, R H., Bauer, W., and Short, C L. Rheumatoid arthritis associated with splenomegaly and leukopenia New England J Med 227 395-399, 1942
16. Bauer, E Ueber die Wirkung der sogenannten Fixationsabscesse Virchows Arch 156: 529-565, 1899
17. Frank, E Aleukia Splenica Berl klin. Wchnschr 53 555-561, 1916
18. Kaznelson, P Verschwinden der hamorrhagischen Diathese bein einem Falle von "essentialler Thrombopenie" (Frank) nach Milzexetirpation Splenogene thrombolytische Purpura Wien klin Wchnschr 26 1451 1454, 1916
19. Reissmann, K. Chronisch agranuloytare Myelopathie also Folge Splenopathischer Markhemmung Med Welt 12 16 20, 1938
20. Wiseman, B K and Doan, C. A A newly recognized granulopenic syndrome caused by excessive splenic leukolysis and successfully treated by splenectomy. J Clin Investigation 18: 473, 1939
21. Wiseman, B K and Doan, C A Primary splenic neutropenia, a newly recognized syndrome closely related to congenital haemolytic icterus and essential thrombocytopenic purpura Ann Int. Med 16 1097-1117, 1942
22. Doan, C A Hypersplenism Bull N Y Acad Med 25 625-650, 1949
23. Dameshek, W Leukopenia and agranulocytosis Oxford Looseleaf Medicine 2 848, 1944
24. Hutchison, H E., and Alexander, W D Splenic neutropenia in Felty's syndrome Blood 9 986-1007, 1954
25. Curtis, A C and Pollard, H M Felty's syndrome; its several features including tissue changes, compared with other forms of rheumatoid arthritis Ann Int Med 13 2265, 1940
26. Hutt, M S R, Richardson, J S and Staffurth J S Felty's syndrome A report of four cases treated by splenectomy Quart. J Med 20 57 73, 1951
27. Fitz, R Three cases with intermittently painful joints, splenomegaly and anemia M Clin North America 18 1053 1066, 1935
28. Singer, H A and Levy, H A Relationship of Felty's and allied syndromes to sepsis leta Arch Int. Med 57 576-600, 1936
29. Williams, R A Felty's syndrome, report of a case with necropsy findings Ann Int. Med 9 1247 1255 1935
30. Hatch, F. N Atrophic arthritis associated with splenomegaly and leukopenia Ann Int. Med 23 201 220, 1945
31. Cudkowicz, L Felty's Syndrome Rheumatism 12 37-41, 1956
32. Ferhstand, J B, and Holsapple, C Rheumatoid arthritis with neutropenia and splenomegaly (Felty's syndrome) with improvement after splenectomy Texas State J Med 46 842-845, 1950
33. Kanar, E A., Harkins, H N., Crone, R I, Lyter, C S, and Robinson, A H Felty's syndrome report of two cases treated by splenectomy West J Surg 58 670-681, 1950

34 Rogers, H M and Langley, F H · Neutropenia associated with splenomegaly and atrophic arthritis (Felty's syndrome), case in which splenectomy was performed. Ann. Int Med. *32* 745-754, 1950

35 Rovello, F. Felty's syndrome; clinical and therapeutic remarks. Rheumatism 6 149-156, 1950

36 Smith, S and McCabe, E S. Primary splenic neutropenia with arthritis (so-called Felty's syndrome), treatment with splenectomy. Ann. Int. Med *29*· 415-455, 1948

37 Ellman, Philip, Cudkowicz, Leon, and Elwood, J. S Therapy of "Felty's Syndrome" Ann Rheu Dis *14*. 84 88, 1955.

38 Schoch, E P., Jr Ulcers of the leg in Felty's Syndrome. Arch Dermat & Syph *66*· 384, 1952

39 McCabe, E S. Felty's Syndrome. J. Insur. Med *13* 80, 1951

40 Craven, E B. Splenectomy in chronic arthritis associated with splenomegaly and leukopenia (Felty's Syndrome) J A M A *102*: 823 826, 1934

41 Bichel, J and Kissmeyer-Nielsen, F Felty's Syndrome treated with ACTH Acta haematol *6* 65-70, 1951

42 Hanrahan, E. M and Miller, S R The effect of splenectomy in Felty's Syndrome J A M A *99* 1247-49, 1932.

43 Hirschboeck, J S Haematologic effects of splenectomy in Still Chauffard Felty syndrome A report of two cases Blood *1*: 247-255, 1946

44 Price, A E and Schoenfeld, J B Felty's syndrome Ann Int. Med *17*: 26-40, 1942.

45 Nystrom, G Om Felty's syndrome i anslutning till ett splenectomerat fall Nord Med *32* 2567 2570, 1946

46 Stodtmeister, R Knochenmarksinsuffizienz Splenomegalie und chronisch-intestinelle Hepatitis bei primar chronischer Polgarthritis eine besondere Auspragung des Felty-Syrondromes. Folia haematol *70* 209-212, 1950-51.

47 Trolle, E and Trolle, D Two rare forms of splenomegaly; chronic polyarthritis with splenomegaly (Felty syndrome) and nonparasitic cysts of spleen Nord Med *18* 761-766, 1943

48 Zimmer, J Felty's syndrome splenomegalia, leucopenia and polyarthritis familial occurrence Acta med Scandinav. *12*. 543 567, 1945.

49 Smith, S. and McCabe, E S. Primary splenic neutropenia with arthritis (so-called Felty's syndrome) Its treatment by splenectomy Ann. Int Med *29* 415-455, 1948

50 Sugarman, H and Balzan, D M Primary splenic neutropenia with rheumatoid arthritis (Felty's syndrome) Canad M A J *63*· 72 74, 1950

51 Wilson, W H and Hamilton, A T Splenectomy as method of treatment in a case of Felty's syndrome South M J *44* 902-904, 1951

52 Langston, W, White, A O and Ashley, J F. Splenic neutropenia report of a case with splenectomy Ann Int Med *23* 667 672, 1945

53 Holland, C W: The value of splenectomy in haematological disorders Canad M A J *59* 13 18, 1948

54 Palumbo, L T Primary splenic neutropenia a specific indication for splenectomy Report of a case Ann Surg *129* 131-136, 1949

55 Bach, J and Jacobs, J H Splenectomy in rheumatoid arthritis Ann Rheumat Dis *10* 320, 1951

56 Welch, C S and Dameshek, W. Splenectomy in blood dyscrasia New England J Med *242* 601-606, 1950

57 Gauld, W Hypersplenism with arthritis Report of a case Lancet *2*· 989 991, 1949.

58 Auger, C., Jobin, J B and Larochelle, L. N. Subacute neutropenia treated by splenectomy Canad M A J 53 335-341, 1945
59 Peden, J C., Hypersplenism: two cases with leg ulcers treated by splenectomy Ann Int Med 30 1248-1262, 1949
60 Steinberg, C L: The value of splenectomy in Felty's Syndrome Ann Int Med 17, 26-40, 1942
61 Smith, P. E: Hypophysectomy and replacement therapy in rats Am J Anat 45: 205, 1930
62. Perla, D. Relation of the hypothesis to the spleen J Exper Med 30 599, 1936
63. Friedgood, H F: The effect of an alkaline extract of the anterior hypothesis upon the weight of the spleen and adrenal gland and upon the blood calcium level Endocrinology 20 159, 1936.
64 Waugh, T R: Acquired hemolytic jaundice in a woman previously splenectomized for essential thrombocytopenia Folia haemat. 48 248, 1932
65 Hargrave, M M: Production in vitro of the L. E cell phenomenon, use of normal bone marrow elements and blood plasma from patients with acute disseminated lupus erythematosus Proc Staff Meet., Mayo Clin 24 234, 1949
66 Unpublished data
67 Ishmael, W. K Acute monocytic leukemia Report of a case treated with cortisone and 6 mercaptopurine South M J 49 553, 1956
68 Salzer, M, Ranschoff, J L and Blatt, H Primary splenic neutropenia with report of a case Ann Int Med, 22: 271, 1945
69 Alt, H L "Discussions." J Lab & Clin Med 30 386, 1945
70 Brugsch, Heinrich G Rheumatic Diseases Rheumatism and Arthritis Philadelphia, Lippincott, 1957
71 Unpublished data

Rheumatoid Spondylitis* (Ankylosing Spondylitis, Marie-Strumpell Disease, Von Bechterew's Disease, Pelvo-Spondylitis Ossificans)

by Harry Edward Thompson

IN DISCUSSING RHEUMATOID SPONDYLITIS, I have tried to present the subject briefly. For the interested reader, a review of the current literature and a complete bibliography from 1952 to 1957 are included. Conflicting, controversial, or not yet established therapy, and some of the subject material covered elsewhere in this book have been omitted in the discussion.

Rheumatoid spondylitis has essentially the same probable causes, constitutional symptoms, pathology, and laboratory and x-ray findings as rheumatoid arthritis; differences are found in the *incidence*, the *physical findings*, the *course*, and the *treatment* of the disease.

REVIEW OF THE LITERATURE WITH REFERENCE TO FAMILIAL OCCURRENCE, HEREDITARY FACTORS AND INCIDENCE

The familial occurrence and heredity factors of rheumatoid spondylitis have been elaborated by Stecher,[1,2] Stecher and Hersh[3] and Selinkoff and Miller[4] in the United States, and elsewhere by Ravault, Traeger and Touraine,[5] Vacrinos and Papadakis,[6] Huttlova and Niepel,[7] and Jacobs and Rose.[8] The more frequent occurrence in males as compared to females was again stated, but there appeared some reported differences in the ratio of males to females affected. Brown and Abbatt[9] in England reported a ratio of 5.95 to 1.0 among 9364 cases, while Polley[10] reported from the Mayo Clinic in the United States a ratio of 9 to 1 in 1035 cases, and Parr, White and Shipton[11] in 1951 reported a male-female ratio of approximately 6 to 4. This was from Australia, where there is a predominately female population. Nearly all contributors included both sexes in their studies, but two reports of rheumatoid spondylitis in women appeared by Tyson, Thompson and

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Ragan,[12] and Ravault, Berthier and Dupré[13] and in the Medical Journal of Australia [14] The onset of rheumatoid spondylitis was found generally to occur most commonly between the ages of 20 and 40 years by most workers, but Barkin, Stillman and Potter,[15] Luechesi,[16] Lynn[17] and Ziff, Conteras and McEwen[18] have drawn attention to the rather frequent involvement of the spine in juvenile rheumatoid arthritis

Discussion

One of the peculiarities of rheumatoid spondylitis is the high incidence of the disease in males, as compared to females This ratio has been reported from 10 to 1, 6 to 4, and 4 to 1. The ratio variance may be due to the locality and possibly to the population ratio of males to females Spondylitis has a tendency to affect the well built muscular male The most common age of onset ranges from 20 to 40 years I have seen patients under 12 and over 50, when the disease developed; no doubt it may occur at any age. Involvement of the spine is frequent in juvenile rheumatoid arthritis

REVIEW OF THE LITERATURE WITH REFERENCE TO EARLY DIAGNOSIS, PHYSICAL FINDINGS, AND THE COURSE OF RHEUMATOID SPONDYLITIS

The early diagnosis and signs of rheumatoid spondylitis were stressed in many papers [10, 19-26] Freyberg and Rogoff[12] and Crenshaw and Hamilton[28] drew attention to rheumatoid spondylitis as a cause of backache Fletcher and Rose[29] call attention to the fact that psoriasis may be a sign of existing spondylitis Many excellent clinical studies in rheumatoid spondylitis have appeared [30-45] Blumberg and Ragan[46, 47] reported on the natural history of rheumatoid spondylitis in 311 patients, of whom they were able to follow 102 They noted that while the disease usually progressed relentlessly (though not necessarily), good functional capacity (class I) was maintained in approximately 75 per cent of the patients The relentless progress of the disease over a 20-year period, with a description of the history and post-mortem findings in a man with rheumatoid spondylitis, was described by Gilmore and Stecher [48] Polley[10] reported the variable clinical pattern and other features of rheumatoid spondylitis. Sharp and Easson,[49] in their study of 332 cases of rheumatoid spondylitis, noted that 242 were typical, 59 atypical and 31 borderline This division as to type was important, since the response to treatment was variable. False,[50] masked[51] and atypical[52, 53] rheumatoid spondylitis were described Ankylosing spondylitis and N Fressinger-Leroy-Reiter Disease were described [54, 55]

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The *physical findings* that predominate early in typical rheumatoid spondylitis are characteristic involvement of the sacro-iliac joints and lumbar

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progress Throughout the course, the patient has fair to good functional capacity.

This is the usual course of rheumatoid spondylitis in a patient who is *untreated* Attention is called to several features not usually found in peripheral arthritis (1) the characteristic remissions and reversal of symptoms; (2) the transitory involvement of peripheral joints; (3) the lack of permanent peripheral joint involvement; and (4) the retention of some functional capacity In contrast with the usual course, there are some patients who have no pain, some in whom the disease may be localized only in the sacro-iliacs or lumbar spine, or dorsal or cervical spine; some patients in whom the disease may skip segments of the spine and be found in the sacro-iliac area and in the cervical spine; some patients in whom ankylosis appears very rapidly, and some patients in whom multiple peripheral joints are permanently involved while the disease is progressive, severe and disability complete. The course of rheumatoid spondylitis can be changed or modified in most patients by treatment. Success is predicted upon early diagnosis and early institution of therapy

REVIEW OF THE LITERATURE WITH REFERENCE TO TREATMENT OF RHEUMATOID SPONDYLITIS

Treatment of rheumatoid spondylitis was reviewed by many contributors.[10, 59-75] Rest, exercises and various types of physical therapy were advocated [78-80] Symptomatic measures and methods to prevent deformities were stressed The correction of deformities in rheumatoid spondylitis was reviewed in several papers [87-93] Lichthlau and Wilson [94] stated that "rheumatoid spondylitis, if allowed to progress, becomes a tragedy, permanently disfiguring and disabling At this stage the treatment falls within the realm of the orthopedist. To date the best treatment of deformity lies in the field of prevention" Various orthopedic procedures were recommended or carried out for the correction of deformity of the spine (i e, osteotomy of the lumbar vertebra)[95-102] and for the hip (i.e., acrylic or other arthoplasty.[103-107] Operations to improve the weight-bearing angle of the femur (i.e., femoral osteotomy) were described [108] Some orthopedic procedures were followed by complications such as adrenal-cortical insufficiency following manipulations,[109] aortic rupture following manipulation of the spine under general anesthesia,[94] fracture,[110] and dislocation.[111] Two spondylorometers were described, one by Thomas,[112] the other a Spondylorometer by Gaspondinoff[113] for measurement of the curvature and rotation of the spine in rheumatoid spondylitis The need for corsets and their application has been described.[114]

X-ray therapy was evaluated [115-123] Sharp and Easson[40] found in a series of 332 cases of rheumatoid spondylitis given 1500r's, that the response in typical cases (149 out of 212 were much improved) was better than in the

spine with a typical loss of the lumbar curve and paravertebral muscle spasm, with limitation of spinal mobility, with objective signs of pain and tenderness on motion, usually with involvement of spinal nerves as manifested by sciatica and radiculitis and with permanent involvement of the hip (in 20 to 30 per cent of the cases). While hip joints are involved, as noted above, other peripheral joints seldom are the sites of a permanent arthritis. Heat and swelling usually demonstrable in peripheral rheumatoid arthritis are not found in the spine. Late in the disease, the findings are ankylosis, flexion of the dorsal spine, immobility of the rib cage and other signs of the disease, weight loss, muscle atrophy and disability In a few instances, there are evidences of localization of the disease in one segment of the spine or sacro-iliac joints, i.e., it may be localized only in the sacro-iliac joints or in the lumbar, the dorsal, or the cervical spine This is in contrast to the usual findings of combined involvement of sacro-iliac joints, lumbar, dorsal and usually cervical spine. The physical findings, symptoms and signs are otherwise those found in peripheral rheumatoid arthritis.

The *course* of rheumatoid spondylitis is unlike that of peripheral rheumatoid arthritis in many respects In fact, because some of the differences are so marked, a few of our colleagues believe that rheumatoid spondylitis and rheumatoid arthritis are separate diseases. One might expect differences to exist when rheumatoid arthritis occurs in the spine. There are, in the spine, many articular structures and adjacent articulations. Many are in close relation to nerves and nerve trunks. Present also in the spine are many postural and weight-bearing stresses.

Before the differences are discussed, a typical course of rheumatoid spondylitis may be described. The disease usually begins in a young adult male; pain and stiffness, "like lumbago," appear in the low back. There is tenderness over the sacro-iliac joints and over the paravertebral muscles, as well as spasm. The normal lumbar lordosis has flattened. The patient has difficulty getting out of bed and standing up. These findings are usually transitory and reversible. They may be relieved by walking and exercises, only to return later Stiffness after rest is usual. Radiculitis and sciatica may be present. Next may appear the persistent signs. Physical examination reveals either permanent loss or marked limitation of motion in the lumbar area Other signs of the disease appear—weight loss, weakness, fatigue, etc. The disease then tends to travel upward, including first the dorsal, then the cervical spine. Transitory involvement of the peripheral joints appears (and disappears). Bony ankylosis and ligamentous calcification may appear to make the spine rigid and the rib cage immobile. Tendency to flexion increases as the disease progresses, and bowing and tortion of the dorsal spine may be pronounced * Permanent involvement of hips may appear and

*Measurement of height and chest expansion at regular intervals is indicated

progress. Throughout the course, the patient has *fair* to good functional capacity.

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atypical cases (11 out of 59 were much improved). Similar findings were reported by the Empire Rheumatism Council (1954-55) in 500 cases of ankylosing spondylitis treated by x-ray. This series revealed, according to Kellgren,[115] that since x-ray was not beneficial to atypical cases and there was a risk of leukemia and anemia, it be withheld There have been some studies which indicate leukemia may be induced by radiation therapy. Brown and Abbatt,[9] who surveyed 9364 patients with rheumatoid spondylitis treated by x-ray, *estimated that on a statistical* basis the death rate (from leukemia) was greater than 5 times and possibly 10 times the number of expected deaths in these patients. From this data there was evidence that patients with ankylosing spondylitis may be unusually susceptible to the development of leukemia, and the incidence of leukemia may be increased among those patients who are re-treated. Radiation leukopenia and aplastic anemia were reported by Goodman[124] and Swaay.[125] The bone marrow was studied prior to and after x-ray therapy by Stewart and Dische.[126] They report the findings in a study of the bone marrow in 28 cases of ankylosing spondylitis. The marrow prior to therapy was hypercellular in 39 per cent of these, and normal in the remainder. Following treatment with x-ray (1020-1640r), aplasia of the marrow was noted in all cases (2 days to 6 months later). Marrow examinations 15 months to 14 years later exhibited regeneration, usually incomplete. Seven of 10 bone marrows were aplastic or hypoplastic. They noted also that marrow changes distant from the site of treatment were transient Polley[10] has drawn attention to the possible effect on ovarian activity in premenopausal women. Permanent amenorrhea was *reported to have* occurred in 13 out of 47 females by Sharp and Easson.[49] There were no reports in the United States of leukemia in rheumatoid spondylitis patients following x-ray therapy Most investigators[37] have verified the favorable response of patients with rheumatoid spondylitis to irradiation. Attention is called to the smaller total dose generally used in this country (600 to 800r) (Boland),[145] as compared to the larger doses (1050-1500r) given elsewhere.[49, 115]

Drugs employed in the treatment of rheumatoid spondylitis received attention in the literature, particularly corticotropin, corticosteroids, and phenylbutazone Many investigators[81-91, 125-146] studied the adrenocorticosteroids. Boland[127] preferred to use steroids as second choice, reserving them for those patients who fail to respond to roentgen therapy and general measures. Long-term therapy with these agents was reported.[134-140] Hydrocortisone was injected intrathecally in 18 patients with rheumatoid spondylitis. Only four patients required a second injection for relief of radicular pain. The *author*[141] noted that equal relief was obtained by injecting normal saline! There appeared general agreement (1) that the adrenocorticosteroids should be given only for short periods of time; (2) that if given continuously,

small optimal doses are indicated, and (3) that they do not prevent the progress of the disease. In other words the indications for these steroids in rheumatoid spondylitis appear to be the same as those for rheumatoid arthritis elsewhere in the body.[10] Phenylbutazone was mentioned in nearly all reports and evaluated in many[142, 144-152] for the treatment of rheumatoid spondylitis Holbrook[141] found phenylbutazone a drug of choice in rheumatoid spondylitis; the results were superior to those secured with x-ray therapy. He noted no progression of the disease either by clinical or x-ray evidence in those patients maintaining improvement with the drug (total number not specified) However, Meyer[149] was seldom able to find any objective improvement in 161 patients treated with phenylbutazone, although considerable relief of pain was observed In most reports on phenylbutazone, its pain relieving properties were noted,[128, 129 141-151] its toxicity recorded,[141] and its failure to prevent progression of the disease acknowledged. Studies of phenylbutazone, plasma concentration and urinary excretion were recorded.[152] Generally, most investigators stressed the administration of safe analgesics (i e., salicylates) and the cautious employment of corticotropin, corticosteroids and phenylbutazone

Discussion

The *treatment* of rheumatoid spondylitis is essentially the same as that for rheumatoid arthritis, which includes treatment of the generalized disease, the attention to constitutional factors, etc Some phases of management are particularly important The physician's approach to this problem, the prevention and correction of deformity, the employment of x-ray therapy and the use of drugs are vital

The physician's approach should be individualized It is necessary for him to modify the treatment to conform to the stage and severity of the disease It may also be necessary at times to modify it somewhat in relation to the patient's occupation, his financial status and to the availability of laboratory and x ray treatment facilities. There appears no need to stress the familiar maxim, "There is no cause, there is no cure" Unfortunately, this is interpreted frequently by the patient to mean "there is no treatment" Arrest of the disease can occur in rheumatoid spondylitis! The physician should be optimistic about treatment, since frequent remissions occur in rheumatoid spondylitis—more frequently than in peripheral rheumatoid arthritis He may point out that the functional capacity of these patients is generally greater than that found in peripheral arthritis He can assure the patient that in the majority of cases, treatment is followed by benefit, and in some patients arrest of the disease may be achieved Finally, the physician should prescribe a general conservative plan of treatment

This conservative plan must include measures to prevent deformity

These are bed rest, prescribed exercises (in bed), ambulation and activity, the use of heat and the use of supports This may be achieved, if the disease is acute and severe, by rest in a position of function* on a firm mattress. Heat may be applied externally and intermittently by any means. Graduated exercises in bed, first passive and then active, should be prescribed and begun early. Ambulation and limited mild weight-bearing exercises should be started as soon as possible. Fortunately, the popularity of immobilization of the spine and ankylosis in the position of function has passed. The majority of patients now may retain or regain motion and functional capacity. With graduated prescribed rest plus exercises, they may be rehabilitated. The amount of rest indicated is the amount required to relieve muscle spasm, tendency to flexion and pain. The amount of exercise is judged as that which does not produce pain, fatigue, or muscle spasm. Supports and braces may be employed, but preservation of muscle tone (by exercises) is equally important as preservation of posture by support.

The correction of deformity is less satisfactory than the prevention. In the absence of solid bony ankylosis, some correction may be obtained. The corrective treatment for an ankylosed spine in poor position is surgical. It is limited to lumbar spinal osteotomy. Arthroplasties of the hip joint may aid in the restoration or improvement in the functional capacity of some patients

The employment of x-ray therapy should be considered in the conservative treatment of rheumatoid spondylitis. For some time prior to and since the excellent controlled study of Smyth, Freyberg and Lampe, roentgen therapy has been used with benefit to these patients. Objective signs of success with this modality appear in more than 50 per cent and subjective improvement in more than 70 per cent of the patients treated. Remissions and relief of pain may be achieved, but progression of the disease may not always be stopped. There are no well defined contraindications. At the present time, there appears no direct evidence that this therapy may induce a leukemia. However, it appears desirable that total irradiation not exceed 800r and that the patient be carefully evaluated prior to re-treatment Atypical or borderline cases should not be treated by x-ray. Probably x-ray therapy should be postponed at the onset of a severe acute spondylitis. Some attention should be given to its possible effect upon ovarian activity. There are, of course, patients who respond to symptomatic measures in whom x-ray therapy is unnecessary. Also, there are patients who for other reasons cannot be treated with this modality.

*Feet upright and at right angles (footboard may be used with sandbags beside feet to maintain position), legs extended and in line with the feet, back flat on the bed (a small flat pillow or folded towel may be used under the lumbar curve and under the head, or a plaster half shell to maintain position).

Deep x-ray therapy for rheumatoid spondylitis varies as to the total dose, the frequency of treatment and re-treatment schedule It seems to me that the physician should prescribe the total dose and the areas he wishes treated with the help and advice of the roentgenologist. The roentgenologist should also be responsible for the technic of treatment, i e., he can determine how often these areas are to be treated and in the amounts to reach the prescribed total dose. I prefer to prescribe 800r to the spine rather than a smaller dose, since the smaller dose has seemed less effective and must be repeated more frequently. Irradiation therapy may be repeated if the initial course has been successful. For re-treatment, smaller doses of 350 to 400r may be given to the same areas. Relief may occur in patients immediately or up to six weeks after therapy Occasionally the symptoms are aggravated by treatment before relief occurs. Peripheral joints, when involved, often subside after x-ray therapy to the spine. There appears to be general agreement that x-ray therapy is not effective when applied to peripheral joints

Drugs employed in the treatment of rheumatoid spondylitis are those used in peripheral arthritis. The salicylates, either as aspirin, plain or enteric, 5 to 10 grains (0 3 to 0 65 grams), or sodium salicylate in equivalent dosages given four times daily are indicated as routine Narcotics such as demerol and codeine are not indicated; if used, they should be employed only at short intervals In fact, these drugs do not have the pain relieving properties of aspirin in many instances Phenylbutazone, a dangerous analgesic, has been advocated by some as a drug of choice in rheumatoid spondylitis. Other observers have not been so optimistic because of the high incidence (30-40 per cent) of toxic reactions and the reported deaths due to this drug. However potentially dangerous this drug may be, it seems that in certain patients it may be employed cautiously. For instance, there may be patients in whom x-ray therapy and symptomatic measures have failed, or there may be patients who are unable to obtain x-ray therapy, or there may be patients whose pain cannot be controlled by the intermittent use of steroids or narcotics These, then, are the patients for whom phenylbutazone may be considered Realization that toxic symptoms occur frequently is a prerequisite to therapy. Careful clinical and laboratory examinations are necessary. Limitation of dosage levels to 400 mg. or less per day is indicated. The maximum benefit that one may expect from the drug is subjective relief of pain, since current investigations indicate that no effect on the disease process is achieved

Adrenocorticosteroids are a group of suppressive agents that have only limited use in the treatment of rheumatoid spondylitis. Their employment is limited because usually high dosage levels are necessary to suppress the manifestations of spondylitis, and such large doses are likely to produce

complications. In our studies we have found that the dose level of steroids is directly proportional to the development of undesirable or dangerous complications (i.e., the larger the dose, the greater the incidence of complications). If steroids are employed at high dose levels, they should be given only in short courses. Our observations indicate optimal or maintenance dose levels of these steroids (cortisone, hydrocortisone, prednisone and prednisolone at 40, 20, 7½ and 7½ mg. per day, respectively, for a 120 pound individual) have not been as helpful in rheumatoid spondylitis as in peripheral rheumatoid arthritis. It seems that neither large suppressive doses nor optimal doses of these steroids are indicated in the routine treatment of spondylitis unless several peripheral joints are involved also. Other drugs employed in rheumatoid spondylitis as adjuvants—iron salts, vitamins, etc.—are discussed elsewhere in this book. Attention should be called to the failure of gold therapy in rheumatoid spondylitis.

There are other considerations in the treatment of rheumatoid spondylitis. A change from a rigorous climate for those who are financially able to do so is of value. A change from a strenuous occupation to one less strenuous is helpful. The use of elevators instead of stairs is indicated. Each of these may be considered in the treatment of this disease.

Finally, it is believed that rheumatoid spondylitis is a rheumatoid arthritis of the spine found most frequently in young males. The physical findings and signs are characteristic. The course is usually typical The laboratory findings are as variable as those in peripheral rheumatoid arthritis. The x-rays are diagnostic. Treatment is based upon conservative measures, the treatment of constitutional symptoms, the prevention and correction of deformity, the employment of safe drugs and x-ray therapy. To date, no short cuts are available to patients with rheumatoid spondylitis. With early diagnosis and early institution of therapy, remissions and improvement in functional capacity occur in the majority of patients and in some instances, the arrest of the disease

References

1 Stecher, R M Heredity of arthritis Acta med. Scandinav 154: 318 321, 1956
2 Stecher, R. M Hereditary factors in arthritis M. Clin North America 39, 499 508, 1955.
3 Stecher, R M and Hersh, A H. Familial occurrence of ankylosing spondylitis. Brit J Phys. Med 18: 176-83, 1955
4. Selinkoff, J J and Miller, S. T.. Rheumatic spondylitis; in three members of one family Delaware M J 27: 287-90, 1955.
5. Ravault, P P., Traeger, J and Touraine, R.: Familial forms of ankylosing spondylarthritis Rev rhumat. 20: 516-17, 1953

6 Vacrinos, E. and Papadakis, C.: Familial form of ankylosing spondylarthritis. Rev. rhumat 22 835 7, 1955
7 Hüttlova, O and Niepel, G. A Cases of familial outbreak of spondylarthritis ankylopoietica Brat Lek Listy 31 290-3, 1954
8 Jacobs, J H and Rose, F C: The familial occurrence of ankylosing spondylitis Brit M J 2 1139-40, 1954
9 Brown, W M C. and Abbatt, J D: The incidence of leukemia in ankylosing spondylitis treated with x rays, a preliminary report Lancet 268 1283 5, 1955
10 Polley, H F. The diagnosis and treatment of rheumatoid spondylitis M Clin North America 39 509 28, 1955
11 Parr, L J A., White, P., and Shipton, E Some observations on 100 cases of ankylosing spondylitis. M J Australia 1 544, 1951
12 Tyson, T. L, Thompson, W A L, and Ragan, C Marie Strumpell spondylitis in women Ann Rheum. Dis 12 40-2, 1953
13 Ravault, P, Berthier, L., and Dupre, A L. Female spondylarthritis ankylopoietica with slow onset Lyon Med 86 533 7, 1954
14 Ankylosing spondylitis in women Editorial M.J Australia 40 308 9, 1953
15 Barkin, R E., Stillman, J S, and Potter, T A The spondylitis of juvenile rheumatoid arthritis New England J Med 253 1107 1110, 1955
16 Lucchesi, M and Lucchesi, O Contribution to the study of infantile rheumatism, rheumatoid or ankylosing spondylitis in children Reumatismo 8 130-6, 1956
17 Lynn, T. N, Rheumatoid spondylitis in a prepubertal female Am J Dis Child 91 158-61, 1956
18. Ziff, M C., and McEwen, C Spondylitis in post pubertal patients with rheumatoid arthritis of juvenile onset Ann Rheum Dis 15 40-45, 1956
19 Lyons, A R Early diagnosis and treatment in ankylosing spondylitis Ulster M J 23 34-8, 1954
20. Sedin, N S: Early diagnosis of ankylosing spondylarthritis Ortop Travm Protez Moskoa 5 30 5, 1955
21 Herzog, R Experiences and observations in therapy of Bechterew's disease Ztschr. f Orthop 84 70 6, 1953
22 Hubault, A Symptoms of onset of ankylosing spondylitis Concours Med 76 2871-4, 1954
23 van der Meer, P Clinical aspects of Bechterew's disease with special reference to early symptoms Nederl tijdschr v geneesk 98 2686-7, 1954
24 Cheshire, D J and Nichols, P J The early stages of ankylosing spondylitis. Rheumatism 11: 79-82, 1955
25 Mendelek, V Early diagnosis of ankylosing spondylarthritis Rev méd Moyen Orient 12 361 5, 1955
26 Persons, E L. and Baker, L. D Ankylosing spondylitis GP 8 83-8, 1953.
27 Freyberg, R H and Rogoff, H B Diagnosis of the common causes of backache (rheumatoid spondylitis) M Clin North America 38 660-62, 1954
28 Crenshaw, A H and Hamilton, J F Rheumatoid spondylitis South M.J 45: 1055-1060, 1952
29 Fletcher, E and Rose, F C Psoriasis spondylatica Lancet 268 695-6, 1955
30 Baker, L. D Marie-Strumpell arthritis Am Acad Orthop Surgeons, Lect. 10 122 130, 1953
31 Harley, J B Rheumatoid spondylitis, a review of 105 cases West Virginia M J 52 301-4, 1956

32 Hart, F. D and Maclagan, N F.· Ankylosing spondylitis; a review of 184 cases Ann Rheumat Dis *14*· 77-83, 1955
33 Baker, L D : The diagnosis and care of Marie-Strumpell arthritis. Postgrad. Med *15* 428-36, 1954
34 Lucherini, T and Cervini, C Problem of ankylosing spondylitis Reumatismo 8 1 36 36-40, 1956
35 Ward, W. R : Discussion on some aspects of ankylosing spondylitis, review of 93 service cases Proc Roy. Soc Med *48*. 210, 1955
36 Rocha, M Spondylarthropathies, concept, description and classification Rev Brasil Med *10*· 712-7, 1953
37 Druckman, A, and Frankel, M Spondylitis ankylopoietica, a contribution to its definition and etiology. Acta med orient *14*· 33-43, 1955
38 Baird, J P Discussion on some aspects of ankylosing spondylitis, symptoms and diagnosis Proc Roy Soc Med *48*· 201-4, 1955.
39 Hart, F D Ankylosing spondylitis, a survey Ann Rheumat Dis *13* 186 9, 1954
40 Galli, T. Ankylopoietica spondylitis Reumatismo *5*· 12-19, 1953
41 Cervini, C and Longo, C.· Nosography of rheumatoid arthritis and variations (especially ankylosing spondylitis, clinical study). Policlinico (sez prat) *60* 1041 1052, 1953
42 Demeulenaere, L · Bechterew's disease Belg. tijdschr. geneesk *9* 1073-88, 1953
43 Weissenbach, R · Ankylosing spondylitis France méd *16*, 15 22, 1953
44 Aufdermaur, M Spondylitis ankylopoietica, Bechterew Aerztl Wchnschr. *8* 1089-94, 1953
45 Robecchi, A and Mussa, L. Ankylosing sacroileitis Minerva med *47* 1319 26, 1956
46 Blumberg, B and Ragan, C The natural history of rheumatoid spondylitis Bull Rheumat Dis *6* 95 6, 1955
47 Blumberg, B and Ragan, C The natural history of rheumatoid spondylitis Medicine *35* 1 31, 1956
48 Gilmore, H R, Jr and Stecher, R M Rheumatoid arthritis and spondylitis; the clinical history and the pathological changes after twenty years of disability Mil Med *117* 432-8, 1955
49 Sharp, J and Easson, E C, Deep x ray therapy in spondylitis Brit MJ *1*· 619 23, Mar 13, 1954
50 Forestier, J and Certocmy, A. False polyarthritis rizomelic Reumatismo *6*: 137-47, 1954
51 Marticke, G Masked late forms of Bechterew's disease Deutsche med Wchnschr. *79* 507-9, 1954
52 Pawelke, K and Schoger, G A Atypical forms of Morbus Bechterew Arztl. Wchnschr *10* 210-2, 1955
53 Ory, M and Henrard, A : A rare form of ankylosing spondylarthritis Rev Rhumat Par *21*· 347-9, 1954
54 Marche, J : Ankylosing spondylitis and syndrome of N Frissinger-Leroy-Reiter France méd *18* 43-7, April, 1955
55 Marche, J Ankylosing spondylitis and Frissinger Leroy-Reiter syndrome; two aspects of the same rheumatismal disease France méd *18* 7 30, Jan, 1955
56 Marche, J Spondylitis ankylopoietica and the Frissinger LeRoy Reiter syndrome; two aspects of the same disease France med *18* 5 32, Feb, 1955
57 Natale, P and Scripilliti, S : Genitourinary infections and ankylosing spondylitis. Progr med Napoli *11* 545 54, 1955

58 Marche, J Fissinger Leroy Reiter syndrome and ankylosing spondylarthritis, relationship and nosology Rev Rhumat. Par 21 321-8, 1954
59 Smyth, C. J · Rheumatoid spondylitis, its diagnosis and treatment South Dakota J. Med 6· 347-350, 1953
60 Robles, Gil J and Zamudio, L. Clinical picture of rheumatoid spondylitis, study of 50 patients Gaceta med Mexico 86 85 92, 1956
61 Ravelli, A · Patho genesis of the so called Bechterew's disease Med Klin 51 758-61, 1956
62 Ruffie, R and Fournie, A Ankylosing spondylitis Toulouse med 55 775 99, 1954
63 La capére, J Ankylosing spondylitis Semaine d hôp Paris 31 2656-62, 1955
64 Camera, R and Broger, E Study of the etiology of ankylosing spondylitis Bechterew Marie-Strümpell disease) based on 215 cases hospitalized at the Rizzoli Orthopedic Institute Minerva ortop 6 434 8, 1955
65 Romanus, R Pelvo spondylitis ossificans in male (ankylosing spondylitis, morbus Bechterew-Marie Strumpell) and genitourinary infection, etiology significance of latter and nature of disease based on study of 117 male patients Act med Scandinav 145 1 368, 1953
66 Houli, J. Treatment of ankylosing spondylitis Med cir farm 234 442 57, 1955
67 Engfeldt, B, Romanus, R and Yden, S Histological studies of pelvo-spondylitis ossificans (ankylosing spondylitis) correlated with clinical and radiological findings Ann Rheumat Dis 13 219 28, 1954
68 Houli, J. Clinical study of rheumatoid arthritis, ankylosing spondylitis and rheumatic fever Arq brasil med 45 15 34, 1955
69 Hart, F D · The treatment of ankylosing spondylitis Proc Roy Soc Med 48 207 10, 1955
70 Hart, F D Ankylosing spondylitis Schweiz med Wchnschr 83 786-8, 1953
71 Mathieu Pierre-Weil, Sichere, R M, and Jean, J Evolutine rheumatism, or rhizomelic spondylosis Rev Rhumat. Par 20 36 8, 1953
72 West, H F. Ankylosing spondylitis Med Illust 9 521-6, 1955
73 Pagowska-Wawrzyńska, J Review of therapeutic methods used in primary chronic rheumatism and in ankylosing spondylitis Polski arch med Wewn 24 649 80, 1954
74 Aufdermaur, M Findings in spondylitis ankylopoietica Bechterew Schweiz. Ztschr f allg path. 16 1009 11, 1953
75 Hubault, A Sacroiliac arthritis in ankylosing spondylarthritis Rhumatologie 5 189 92, 1955
76 Stephenson, W H The management of ankylosing spondylitis Physiotherapy 41 109 11, 1955
77 Yvanoff· Ankylosing spondylitis Acta physiother rheumat, belg 10 33 5, 1955
78 Yeoman, W The place of physiotherapy in the treatment of the rheumatic disorders. Brit J Phys Med 18 76-81, 1955
79 Complex balenotherapy of Bechterew's disease Acta chir orthop traum, Editorial Cech 20 175 83, 1953
80 Bruhl, W Evaluation of results of balneologic therapy rheumatism according to 6 month observation of 100 cases at Ciecpocinek Postepy Reumat 1 207 20, 1954
81 Hasik, J Ultrasonic therapy of ankylosing spondylitis and arthritis deformans of the spine Polski arch med Wewn 24 937-41, 1954
82 Nunes, C V Rheumatoid spondylitis, pathological anatomy and therapy Med cir, farm 207 281 94, 1953

83. Pagowska-Wawrzyńska, J and Grajnert, K: Effect of mud packs on 17 ketosteroids in urine and on eosinophil count in ankylosing spondylitis Postepy Reumat. 1: 126-36, 1954

84 Polaková, Z., Popelka, S., Truhlar, P., Zámostná, M., Hájková, Z., Hnérkovský, O., Kadlcová, L., Kralik, V., Lennogh, F., Nechvátalová, L., and Pauerová, V., Exercise therapy in ankylosing spondylitis; active exercises. Fysiat. Vest., Praha. 31: 115-31, 1953

85 Polaková, Z., Popelka, S., Truhlár, P., Hartová, E., Nechvátalová, L., Pauerová V., Zamostna, M., Králik, V., Lennogh, F., Hájková, Z., Hnérkovský, O., and Kadlecová, L.: 1 Physical therapy in Bechterew's disease; 2 Passive exercises Fysiat. Vest., Praha. 32: 72-86, 1954.

86 Hájková, Z and Truhlar, P: Effect of regular physical exercises on the development of ankylosing spondylitis. Fysiat. Vest, Praha. 31: 109-15, 1953

87 Sanchis Olmos, V. Orthopedic treatment and surgery of ankylosing spondylitis Clin Laborat Zaragaza 58. 1-9, 1954.

88 Pais, C. Surgery of ankylosing spondylitis. Chir. org movim 42. 479-532, 1956

89 Pais, C Surgery of ankylosing spondylitis Rheumatismo 8 41-58, 1956.

90. Cerveňanský, J. Considerations on surgical treatment of Bechterew's disease. Acta chir orthop traum, Cech 22 126-34, 1955

91. Swaay, H Van Anatomic changes in spondylosis deformans and spondylosis ankylopoietica Nederl. tijdschr v. geneesk. 98: 2631-6, 1954

92 Charles, Symonds The interrelation of teguma and cervical spondylosis in compression of the cervical cord. Lancet 1: 451-54, 1953.

93. Dupuis, P V Functional study of some results of operations for bilateral ankylosis of the hip complicating rhizometic spondylosis, three year follow up Acta orthop, belg 19: 395-6, 1953

94 Lichtblau, P. O and Wilson, P D Possible mechanism of aortic rupture in orthopedic correction of rheumatoid spondylitis J. Bone & Joint Surg. 38: 123-7, 1956

95. Skotnicki, Z Osteotomy in the treatment of ankylosing spondylitis Chir. Narg Ruchu ortop polska. 18 201-7, 1953.

96 Renovales, and L Bellón Osteotomy; correction of kyphosis in ankylopoietic spondylitis Med y segur Trab 1: 46-59, 1953.

97 Pap, K: Correction of spinal crookedness in Bechterew's disease through paracolumnarosteotomy. Zbl Chir 80 1127-9, 1955

98 Botelheiro, J: Cuneiform osteotomy in kyphosis due to spondylitis ankylopoietica; clinical case Acta ortop traumatol Ibér 1. 131-134, 1953

99 Del Torto, P Vertebral osteotomy Riforma. med 69: 453-8, 1955

100 Fortier, M, Hebert, H., Technic of vertebral osteotomy in correction of rhizomelic spondylosis Union méd du Canada 82: 1109-13, 1953

101 Herbert, J J., Paillot, J Technic and results of vertebral osteotomy; observations on 35 cases Rhumatologie 4: 246 66, 1953

102 Starzyk, A Osteotomy of the lumbar vertebra in a case of ankylosing spondyl arthritis. Acta chir jugosl 2. 266-71, 1955

103 Walch, A Presentation of a rhizomelic spondylitis having undergone orthoplasty of the right hip with interposition of an acrylic head and a metallic cup Acta orthop. belg 19: 109-11, 1953

104 Pique, J. A Resection and reconstruction of the hip with acrylic prosthesis in rheumatoid ankylosing arthritis and spondylitis Dia méd 26 747-8, 1954

105 Merle Daubigné, R, Ramadier, J O, and Postel, M. Acrylic orthoplasty in ankylosing spondylitis Rev Rhumat, Paris 22 16 21, 1955
106 Domeniconi, S. Two cases of mobilizing resection of the hip in ankylosing spondylarthritis Reumatismo 8 22-6, 1956
107 Borch Madsen, P Judet's method of bilateral coxarthroplasty in hip ankylosis in spondylarthritis ankylopoietica Ugeskr Laeger 116 500 2, 1954
108 Milch, H Femoral osteotomy in the treatment of Marie Strumpell's disease J Internat Coll Surgeons 20 465 73, 1953
109 Harnagel, E E and Kramer, W G Severe adrenocortical insufficiency following joint manipulation J A M A 158 1518-19, 1955
110 Arosenius, K E Vertebral fracture in pelvo spondylitis ossificans (Morbus Bechterew) 59 p 238 40, Mar 31, 1954
111 Margulies, M E, Katz, I and Rosenberg, M Spontaneous dislocation of the atlantoaxial joint in rheumatoid spondylitis, recovery from quadriplegia following surgical decompression Neurology 5 290-4, 1955
112 Thomas, D A spondylometer Physiotherapy 42 113-4, 1956
113 Gospondinoff, A Spondylorotometer, apparatus for measurement of vertebral rotary movement in ankylosing spondylitis Reumatismo 8 49 51, 1956
114 Godlewski, Z. Need for orthopedic corsets in certain types of ankylosing spondylitis, several proposed types of corsets Postepy Reumat 1 185 93, 1954
115 Kellgren, J H Spondylitis forms responding to x rays in a series of 500 patients Empire Rheumatism Council, Annual Report, 1954 55 J A M A 161 1097, 1956
116 Hilton, G X ray treatment of ankylosing spondylitis Rheumatism 11 10 15, 1955
117, 118 Desmarais, M H L Radiotherapy in arthritis Ann Rheum Dis 12 25-8, 1953.
119 Coste, F and Fauré, C Results and mode of action of x ray therapy in rheumatic disease Semaine d hôp Paris 32 2491 7, 1956
120 Castagnoli, M and Fragale, F S Results of radar therapy in ankylosing spondylitis Reumatismo 8 125 7, 1956
121 Charteris, A A The treatment of haemangioma and ankylosing spondyradiol 116 345 52, 1954
122 Milewicz Z Radiotherapy of spondylarthrosis ankylopoietica (Bechterew's disease) Polski Przegl Radiol 18 29 50 1954
123 Lièvre, J A Spondyloarthritis ankylosing atlas of radiological clinic Presse med 63 1-4, 1955
124 Goodman, G B Radiation leucopenia in ankylosing spondylitis J Fac Radiologist 7 167 71, 1956
125 Swaay, H van Aplastic anaemia and myeloid leukaemia after irradiation of the vertebral column Lancet 269 225-227, 1955
126 Stewart J W and Dische, M Effect of radiotherapy on bone marrow in ankylosing spondylitis Lancet 271 1063 1069, 1956
127 Boland, E W Rheumatoid spondylitis clinical features and current methods of treatment Bull Rheum Dis 11 29 30, 1952
128 Robinson, W D, Boland, E W, Bunim, J J, Crain D C, Engleman, G P, Graham, W, Lockie, L M, Montgomery M M, Ragan C, Ropes, M W, Rosenberg, E F, and Smyth, C J Rheumatism and arthritis Review of American and English literature of recent years Ann Int Med 39 498-618, 757 906, 1953
129 Robinson, William D, Bunim, J J, Clark, W S, Crain, D C, Engleman, E P,

Graham, D C, Montgomery, M. M, Norcross, B M, Ragan, C., Ropes, M W., Rosenberg, E F., and Smyth, C. J Rheumatism and arthritis Review of American and English literature of recent years (eleventh rheumatism review) Ann Int Med 45. 831-945, 1059-1210, 1956

130 Fischer, F and Hastrup B · Cortisone and calcium balance, effect of calcium, vitamin D and methylandrostenedial Acta endro kbh 16 141-8, 1954.

131 DeSèze, R J and Denis, A : The local injection of hydrocortisone in articular and so-called para-articular rheumatism. Rev. Rhumat 20 303 8, 1953

132 DeSéze, S, DeBeyre, N and Bordier, P.· Inflammatory rheumatism and prolonged treatment with Prednisone Bull et mém Soc méd d hôp de Paris 72. 216 226, 1956.

133 Coste, F, Delbarre, F, Massias, P, DeSèze, S, Robin, J, DeBeyre, N, Rubens, Duval, A., and Lacapere, J Results of French tests of metacortandracin in inflammatory rheumatism Rev Rhumat 22· 385-405, 1955

134 Howell, S and Ragan, C The course of rheumatoid arthritis during four years of induced hyperadrenalism (IHA) Medicine 35; 83 119, 1956

135 Lennoch, F and Knobová, J · Therapy of chronic diseases of the joints with cortisone and ACTH on the basis of personal experience. Čas Lék Česk 93. 1121-27, 1954

136 Manuel Losado, L and Juan Zanartu, O · Action of cortisone and corticotropin in rheumatoid arthritis Rev clin españ 49 383-93, 1953.

137. West, H F. and Newns, G R Ankylosing spondylitis and prolonged ACTH therapy Ann Rheum Dis 13· 109 19, 1954

138 Robecchi, A, Daneo, V and Marrazzi, G · Recent clinical and laboratory observations on the treatment of rheumatic diseases with Prednisone with special reference to long term treatment Minerva med 47; 295-305, 1956

139 Bagnall, A W, Traynor, J A and McIntosh, H W The management of Marie-Strumpell spondylitis with special reference to long-term cortisone therapy Canad M A J 68 587-91, 1953.

140 Toussaint, J Long term treatment with cortisone Rev. Rhumat 22: 605-610, 1955

141 Lucherini, T Early results of the intraspinal use of hydrocortisone; preliminary note Rev Rhumat 21 809-16, 1954

142 Holbrook, W P Cortisone, ACTH and phenylbutazone in long term therapy of rheumatoid arthritis M Clin North America 408-9, Mar 1955

143 Coste, F and Chevallier, J Icterus caused by phenylbutazone. Rev Rhumat 21 245 6, 1954

144 Bibawi, E and Mahfouz, M M Clinical evaluation of phenylbutazone (butazolidin) in chronic rheumatic diseases J. Egyt M. 38 342-50, 1955

145 DeSéze, S, Levernieux, J and Carlier, N Phenylbutazone (butazolidin) and ankylosing spondylarthritis, study on 106 cases treated and followed up for from six months to three years Rev Rheum 23. 71-6, 1956

146 DeSéze, S and Levernieux, J Injectable phenylbutazone in rheumatism *Presse méd* 62 203-205, 1954

147 Goldfain, E. Butazolidin in rheumatic diseases J Oklahoma State M. A 46 27-8, 1953

148 Kidd, E G, Boyce, K C., and Freyberg, R H: *Clinical studies of phenylbutazone* (Butazolidin) and Butapyrin (Irgapyrin) in rheumatoid arthritis, rheumatoid spondylitis, and gout Ann Rheuma Dis 12 20 24, 1953

149 Meyer, M P · Butazolidin therapy of rheumatoid arthritis and Bechterew's disease Nederl tijdschr geneesk 99 1546 53, 1955
150 Rego, L. Use of phenylbutazone in rheumatoid spondylitis J Med, Porto 23 537-42, 1954
151 Toone, E. C, Jr and Irby, W R Evaluation of phenylbutazone (Butazolidin) in the treatment of rheumatoid spondylitis report of 50 cases Tr Am Clin & Climat. A 65 77 90, 1953
152 Stanfield, A B, Brodie, E C and Yeoman, E E Butazolidin (phenylbutazone) plasma concentration and urinary secretion in normal individuals in patients with rheumatoid spondylitis Proc Exper Biol & Med 83 254 258, 1953

The Management of Rheumatoid Arthritis

by L. Maxwell Lockie

GREAT STRIDES HAVE BEEN MADE during the past two decades in the management of patients suffering from rheumatoid arthritis. However, since the cause of the disorder is not known, the malady continues to be a challenge to the physician. Until the etiology is revealed, the program of treatment will depend upon the training and enthusiasm of the physician responsible for the patient. The program to be outlined in the present study has been effective in the majority of patients with rheumatoid arthritis treated in this clinic during the past 25 years. Naturally, the milder the disease, the more satisfactory the ultimate results. No matter how advanced the involvement, however, most patients may anticipate good results with retardation of the progression of the disease and thus may enjoy a more comfortable and useful life.

It is necessary that all patients undergo a thorough study initially, even though only a single joint may be involved This entails a detailed history, complete physical examination and the collection of certain laboratory data X-rays are necessary when the signs and symptoms are unusual. At the completion of these studies, which may require a few days, the results of the physical examination as well as the interpretation of the x-ray and other laboratory data are summarized and discussed with the patient. The program is outlined in detail in order to reveal and to clarify what is expected in execution It is desirable to take the patient into full confidence The regimen should be discussed at the same time, when possible, with other members of the family. A written outline is prepared so that the various phases of treatment are well documented. It is stressed that rheumatoid arthritis is a systemic disease and that treatment will be necessary for a long period of time. In this frank discussion with the patient, the general course of the disease is explained with emphasis upon the favorable features, but the more discouraging limitations of treatment must also be mentioned. Even at this point, the patient must be made to understand that he is a member of the team and that his part in the program is essential.

The regimen outlined is especially applicable to those patients who have a mild or moderate degree of arthritis, i.e., class I or II, stage I or II of the disease. However, there are many patients with advanced arthritis who will benefit also. The program is believed to be the one of choice, even though it may seem to be drastic, requiring too much time in a hospital

and to be too expensive. The author is convinced from experience that this type of management will produce good results in 90 per cent of patients.

Ideally, the plan consists of a minimum of three weeks with complete bed rest in the hospital for intensive treatment and education, followed by several months of weekly visits in the office or at home This in turn is followed by additional months of less frequent visits

PRELIMINARY INTENSIVE TREATMENT

Hospital Therapy

Bed rest is *absolutely* necessary for every patient, even those in the earliest, and mildest stage, and is best accomplished in the hospital. A minimum of three weeks is required, only a few patients require a longer period of hospitalization. The patient is seen daily and each phase of treatment is carefully supervised During these visits the physician becomes better acquainted with the patient as the detailed instructions are given regarding the various procedures. The effects of therapy are observed If gold or hormonal medications are used, side effects may be detected quickly when the patient is under such close observation. The physical therapists, nurses and other hospital personnel are also part of the team, one of whose important functions is to teach the patient the many details so important in treatment

No weight bearing is allowed, even though the lower extremities may not be involved. The bed should contain a firm mattress Since an inner-spring or rubber mattress is usually employed, a piece of plywood, ½ inch thick, approximately the size of the bed, is placed between the mattress and the box springs. When a hair, cotton or felt mattress is used, the bed board may make the bed so hard that it is uncomfortable *One* pillow *only* is allowed for the head, thus minimizing or preventing postural deformities of the neck and upper spine It is not necessary for the patient to lie on his back continually, he is permitted to turn in any way to be comfortable. At mealtimes and at three additional periods of the day, it is permissible to sit up for 30 minutes *in bed*, with the back straight. During the remainder of the day, stretching, sleeping and relaxing are encouraged. The use of pillows under the knees has been the most common cause of flexion contractures of the knee joints with crippling Therefore, no pillow is permitted under or between the knees at any time However, a pillow is placed between the bedclothes at the foot of the bed, so that the feet rest against it Thus, the bedclothes come over the top of the pillow, taking the pressure off the toes A footboard may be used with the pillow if desired By this simple procedure, extension deformities with eversion of the feet, formerly seen so often, are prevented The patient is denied bathroom privileges and is not allowed to sit in a chair beside the bed Transportation about the hospital

2½ weeks of hospitalization no weight-bearing exercises are permitted There are several special exercises to be carried out cautiously, designed to improve muscle tone. These instructions are given in detail by the physical therapist The patient is urged to carry out the exercises at regular intervals throughout the day. At no time are any exercises performed which produce pain, but they may be performed up to this point. Contrary to the belief of many, too much exercise is detrimental since the joint linings are tender and inflamed. At no time during the course of rheumatoid arthritis are patients allowed to use any continuous exercise measures, such as knitting, tatting, crocheting or squeezing rubber balls. These repetitious motions aggravate the abnormal underlying process, thus tending to produce more deformities instead of improving the situation. Proper corrective exercises for the patient who is non-weight-bearing and in bed should be started as soon as possible in order to preserve range of motion of the joints as well as muscle tone Full active range of motion of each involved joint is encouraged daily, with muscle exercises as necessary.

Another important duty of the physical therapist is to give instructions to the patient for ambulation toward the end of the stay in the hospital. Well-constructed shoes, not bedroom slippers, are necessary, since the patient has not been bearing weight for several weeks. The amount of walking is regulated according to the ability to carry it out. It is governed by the degree of pain present in the weight-bearing joints. If pain is severe, minimal walking is permitted during the first few trials. In some instances, it is advisable for the patient to use a cane for balancing or even crutches for a few weeks, in order to relieve strain on painful weight-bearing joints. Such support enables the patient to ambulate with better posture. Proper walking patterns are taught when necessary, and, as the patient improves, he is guided day by day as to the amount of physical activity permitted. Before discharge from the hospital, the complete program of exercise and heat to be followed at home should be outlined in detail by the physical therapist. The patient then follows a modified hospital program and returns to normal activity several weeks later in most cases.

Drug Therapy

Salicylates. These are mainstays for pain relief in patients who have rheumatoid arthritis. Aspirin and sodium salicylate are most commonly used in a dosage of 0.6 grams (gr. X) four times a day. Most patients are able to tolerate this dosage for a long period of time with satisfactory pain relief and a few side effects Tolerance does not develop with continuous therapy. Salicylates are effective agents in relieving muscular stiffness, a symptom present in most patients. The intravenous administration of sodium

salicylate is less popular now than formerly Salicylates are of value when used topically in ointment form, as it is one of the few drugs absorbed through the skin If a delayed effect is desired, the administration of salicylates as enteric-coated tablets inhibits absorption several hours. There are some patients who are unable to tolerate salicylates due to gastric irritation; this can be avoided when buffered aspirin tablets are used The action of salicylates is thought to be twofold. One action recently described occurs in the individual cell, in which the fluid content is diminished slightly, thus relieving pain and discomfort The other mode of action is on the thalamus and hypothalamus. It is worthy of mention that occasionally a patient is allergic to aspirin and may experience a severe reaction following ingestion of one or two tablets In summary, the salicylates are considered to be the safest drug to be used for the relief of muscular and joint pain

Analgesics Codeine is not recommended as it produces mental irritability and constipation. It is realized that codeine does relieve pain, in rheumatoid arthritis, however, its effectiveness is overbalanced by the side effects when taken regularly Phenylbutazone (Butazolidin) is a new effective analgesic with a better antirheumatic effect than the salicylates Following its introduction in 1951 for clinical trial, a substantial improvement of joint pain in a large number of cases was observed. Plasma levels are maximum within two hours after an oral dose and within six to eight hours after intramuscular injection It is excreted gradually over a period of from seven to ten days Toxic reactions occur, and in some cases death has resulted The principal complications are edema due to sodium chloride retention, a drug rash which frequently is irritating, activation of peptic ulcers with hemorrhage and perforation and bone marrow depression with agranulocytosis and thrombocytopenia The toxic reactions occur usually when Butazolidin is used in large doses over a prolonged period of time Others may develop toxic manifestations within a day or two, even though small doses are ingested Although its use in rheumatoid arthritis is not clearly defined, it has been found to be of great benefit to some who have derived little help from salicylates The dosage of 100 200 mg per day, which usually can be taken without reaction, has given satisfactory relief to many patients in our clinic They are watched carefully for possible manifestations of toxicity, if such are noted, the drug is stopped at once and permanently

Sedatives Sedation is desirable during the hospital stay in view of the fact that most patients maintain a state of apprehension, in this case small doses of sedatives are given during the day. Occasionally a hypnotic is indicated at night in order to insure a good night's sleep Rest is so vital in this program that every effort is made to achieve it by day and by night As necessary, during the day a small dose of a barbiturate or one of the

tranquillizer drugs is prescribed. For a peaceful sleep, pentobarbital (Nembutal) or secobarbital (Seconal) is given when needed during the hospital stay. The drugs are completely metabolized over a period of from six to eight hours, thus enabling the patient to awaken in the morning refreshed. After hospital discharge most patients do not require hypnotics regularly but may receive benefit if a mild sedative is given during the day for a month or two.

Iron. The degree of anemia usually parallels the severity of rheumatoid arthritis. *Although the effectiveness of iron in the treatment of the anemia* has not been proven, it is accepted practice to prescribe either ferrous gluconate or ferrous sulfate 0.3 Gm. (gr V) three times daily. Ideally, the iron should be given between, not immediately after meals. Patients who have severe anemia frequently derive benefit following transfusion with 500 cc. of whole blood weekly for several weeks. Impressive results have been seen in some patients who suffered from severe active arthritis. The effect appears to inhibit the arthritic process, as well as to correct the anemia.

Gold Salts The employment of gold salts in the treatment of rheumatoid arthritis has been practiced in this country for more than twenty years. Gold salt therapy is the most effective agent in our armamentarium today to stop the progression of arthritis. The mechanism of action is not understood. It is the best controllable medication leading to a decrease in the activity of the arthritis in those who have rheumatoid disease, in the same manner that other toxic agents may diminish objective and subjective arthritic involvement. Recently, the records of 1093 patients who had been under a broad program of management for a minimum period of three months have been studied. The data have been treated statistically and the results noted below are statistically significant. Of 1093 patients, 369 received at least 300 mg. of gold salts during the course of treatment. Gold sodium thiomalate (Myochrysine) was used routinely, although occasionally aurothioglucose (Solganal) was substituted.

Fifty-six per cent of the gold-treated group, with mild involvement, showed major improvement (grades I and II, American Rheumatism Association classification), while only thirty-four per cent of the non-gold-treated controls showed comparable improvement. Sixty-eight per cent of those with moderate involvement showed major improvement (grade I and II) in the gold-treated group, while forty-four per cent of the comparable control group manifested the same degree of improvement. Forty-nine per cent of those with severe disease responded with major improvement (grade I and II), as compared to thirty-five per cent of the controls In the entire group, fifty-seven per cent had major improvement, as compared to only thirty-eight per cent in the controls.

One hundred and thirty-eight patients who received less than three hundred milligrams of gold salts were compared with the same group of controls. There was no statistical difference in improvement of the two groups. Therefore, it is reasonable to assume that if gold salts are to be used effectively as a part of therapy, at least three hundred milligrams should be administered.

Gold and sodium thiomalate (Myochrysine) is available in a multi-dose vial, containing 50 mg per cc in aqueous solution. A 24-gauge ¾ inch needle is used to inject the solution into the deltoid area. The intramuscular deposit is more certain and more convenient than injection in the gluteal region. Not more than one dose per week is recommended, irrespective of the zeal of the physician to expedite treatment. Most reactions to gold occur when it is given more frequently than once weekly, or when large doses are given. The dosage schedule is as follows: 10 mg. the first week, 20 mg the second week; 30 mg the third week, and 40 mg the fourth week. This dose, 40 mg, is given intramuscularly at weekly intervals until a total of from 500 to 750 mg has been administered. At this point a re-evaluation is made, following which the dose is decreased gradually or the intervals between injections lengthened. Patients eventually will be given a small dose, perhaps 10 or 20 mg at monthly intervals for an indefinite period of time, provided no toxic reaction has occurred. When the arthritis becomes inactive, chrysotherapy is discontinued.

Toxic reactions occur but are rarely severe in the carefully observed patient. It is of great importance that before each injection the patient be questioned closely concerning any possible reaction. Certain information to be obtained from urinalysis and blood count studies, collected at regular intervals, also warns the physician if intolerance to the gold salt is developing.

The most common toxic reactions involve the skin, and may vary from mild itching to widespread dermatitis. Glossitis with the characteristic burning sensation along the edge of the tongue and stomatitis, as manifested by a metallic taste of the mucous membranes of the mouth or the feeling that soup which is too hot had been tasted, may appear. Occasionally, thrombocytopenia and agranulopenia are noted in the blood determinations, less commonly, albumin appears in the urine.

Of the total number of 596 patients who had received gold in any quantity, 286 (48 per cent) had some type of reaction with a total of 351 reactions. Only five reactions (2 per cent) were severe enough to require the use of BAL (British Anti-Lewisite, an antidote). It is interesting that fifty per cent of the patients who experience a reaction are able to take more gold, after an interval of from six to eight weeks, when it is administered in small doses. There were no fatalities.

The incidence of reactions in this group occurred as follows:

Reaction	*No. of Patients*
Itching or rash	213
Glossitis or stomatitis	67
Gastrointestinal disturbances	20
Renal disturbances	9
Purpura	17
Thrombocytopenia	11
Local skin reaction	11
Frequency of urination	1
Anemia	1
Anaphylactic	1
Headache	3
Fatal reaction	0

The physician must exercise caution when administering gold salts With reasonable care, however, gold is safe to use at any age, including children There are several conditions which are contraindications to the use of gold salts in any dosage. systemic lupus erythematosus, nephritis, blood dyscrasias and a tendency to hemorrhage.

The urine should be examined every two weeks for red blood cells and albumin. The red blood count, white blood count and blood platelet determinations are checked every four weeks It is interesting to note that the first toxic manifestation upon blood-forming organs may be a decrease in the number of blood platelets. At other times, the granular series of white blood cells may be affected. Any decrease from the normal usually implies immediate cessation of gold salt injections. However, patients have been seen who have had a drop in the number of blood platelets and later have been able to tolerate small doses of gold with improvement in symptoms. A few patients have experienced a marked reaction to the first or second dose of gold; if this is observed, it is important that gold be stopped and not resumed.

The results of treatment of patients with gold is most satisfactory. It is a potent suppressive agent as far as the progression of the disease is concerned and is widely employed in clinics throughout the United States. The mode of action of gold is not understood but it is interesting to note that the closer a patient is to a toxic reaction, no matter how mild, the more marked the improvement The use of gold salts is recommended as an important adjunct to treatment in the management of a patient with rheumatoid arthritis.

Steroids. The use of adrenocorticosteroids and ACTH has been responsible for the tremendous interest in research in the field of rheumatology since 1949 It is realized now that the underlying process in rheumatoid arthritis

not corrected and that the effect of these agents is suppressive There are any patients who need some steroid medication from time to time in the urse of treatment of their disease. It must be carefully supervised at all es and the patients warned not to try to go beyond their physical limita- ons The signs and symptoms can be relieved markedly, temporarily, and it is interesting to note the favorable changes in the synovial fluid as well as in synovial tissue, with changes toward normal in the blood count and blood chemical findings during steroid administration

The following criteria are employed as indications for steroids:

(1) When the clinical status is discouraging to the patient and to the physician, despite faithful adherence to a carefully planned program In such a situation steroids are used in a dosage adjusted as low as possible, in order to give partial relief of symptoms. If the relief were 100 per cent, the dosage would be too high, with the subsequent development of side effects This would be undesirable, since the aim is to alleviate distress without side effects The dosage is individual for each patient and must be adjusted each week or two by the attending physician—the patient should not be permitted to stay on a given dose for a period longer than two weeks Every effort is made to decrease the dose and to discontinue the steroid when it is not necessary for symptomatic relief If side effects develop from small doses, the medication should be discontinued

(2) There are patients who are known to have short-term exacerbations, especially juveniles suffering from rheumatoid arthritis They should be given a corticosteroid during the course of the flare-up It is discontinued gradually as improvement permits.

(3) Patients who experience severe constitutional symptoms, such as tachycardia, pericarditis and high fever, need steroids as life-saving measures Some would not survive without full dosages of steroids

(4) During the rehabilitation of the patient with severe involvement, it is easier to handle the patient and demonstrate the objectives under the suppressive effect of steroids It may be necessary to use the steroids for months in order to accomplish selected objectives in rehabilitation

Corticosteroid therapy will produce the changes of Cushing's syndrome, i.e., obesity, moonface, buffalo hump, hirsutism and acne, if medication is continued long enough and in sufficiently large doses. Sodium retention is not seen as commonly with prednisone and prednisolone as it was with cortisone and ACTH Lowered potassium blood levels are not observed with the newer preparations, but increased blood pressure and hyperglycemia occur occasionally Inasmuch as osteoporosis is a part of the underlying pathology in rheumatoid arthritis, this will worsen with long-term therapy Vertebral collapse, a complication of osteoporosis, usually does not occur unless the corticosteroids are taken a minimum of seven months. This is a serious,

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The urine should be examined every two weeks for red blood cells and albumin The red blood count, white blood count and blood platelet determinations are checked every four weeks. It is interesting to note that the first toxic manifestation upon blood-forming organs may be a decrease in the number of blood platelets At other times, the granular series of white blood cells may be affected *Any decrease from the normal usually implies immediate* cessation of gold salt injections However, patients have been seen who have had a drop in the number of blood platelets and later have been able to tolerate small doses of gold with improvement in symptoms A few patients have experienced a marked reaction to the first or second dose of gold, if this is observed, it is important that gold be stopped and not resumed

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the article by Boland in the present book ("Adrenal Cortical Steroids and some of their Synthetic Analogues in the Treatment of Rheumatoid Arthritis") for a more complete discussion of this subject.

Vaccines The use of vaccines has been discussed in medical periodicals for forty-five years in the treatment of rheumatoid arthritis At the present time, vaccines are not accepted by many rheumatologists However, Cecil isolated a strain of hemolytic streptococci which is agglutinated by the serum of adults who have rheumatoid arthritis. The agglutination may occur even when the serum is highly diluted It is seldom found in the serum of patients suffering from other diseases The significance of this reaction is not clearly understood, but it is an immunologic reaction of relatively high specificity. On this premise, as part of the broad plan of management, those patients who are unable to tolerate gold are given a vaccine of killed hemolytic streptococcus administered weekly in small amounts of 4,000,000 organisms subcutaneously. The dosage is maintained at the same level and is not increased It is my impression that patients who receive vaccine at weekly intervals are improved when comparison is made to those who do not receive it Also, it is appreciated that there is a psychological factor to be considered, but there appears to be benefit gained in addition to any psychotherapeutic component It must not be forgotten that this is only one of many facets which comprise the well-rounded program of treatment.

OTHER FACTORS

Climate has received considerable attention in treatment Obviously, those who are able to enjoy a warm pleasant climate with a shining sun each day *feel better* When the patient moves to a warm climate, either temporarily or permanently, it is highly advisable that a competent physician outline the program of therapy, since without medical supervision the disease may worsen.

Inasmuch as many patients are underweight and undernourished, attempts should be directed toward maintenance of an optimal state of nutrition. There is no specific diet, rather, a *well-balanced diet* should be followed There are no particular foods especially indicated for arthritis, nor are there any to be avoided Food fads are to be condemned Rheumatologists generally are not convinced that there is any special order in which food should be eaten. Every effort should be made to insure that the patient maintains an ideal weight Those who are overweight should reduce, especially if the weight bearing joints are involved Vitamins may be poorly absorbed by the arthritic, but the absolute indication for their use has not been shown in this disease In many instances, patients take vitamins as a result of advertising or following the advice of their neighbors

Foci of infection have been considered since early in the century There

painful complication and is especially prone to develop in postmenopausal women.

Psychological reactions as a result of the corticosteroid or ACTH administration vary from the mild to the severe. It is not possible to predict easily in which patient the changes will occur or their severity. There is some euphoria in all patients who are taking moderate or large amounts of corticosteroids. Their use is contraindicated in the presence of psychoses and in patients with marked psychoneurosis. Two of the most disturbing complications of corticosteroid therapy in our clinic are bleeding and perforated peptic ulcer. It may occur in those who deny symptoms suggestive of an ulcer in the past. The newer steroids, prednisone and prednisolone, seem to be more apt to precipitate these complications than the older steroids Activation of tuberculosis as well as the masking of the signs and symptoms of infections, such as appendicitis and pneumonia, have occurred. Also of great concern is the appearance of pain due to coronary insufficiency. This may be coincidental, but in those in whom it does occur within several weeks after medication is started, it poses the question of aggravation of an underlying process.

Postoperative deaths have followed surgery as the result of shock due *to adrenal insufficiency. It is impossible to determine the extent of adrenal* cortical insufficiency in patients who have taken steroids, nor for what period cortical insufficiency persists following cessation of administration of the drug. Therefore, it is wise to give large doses of hormones just before, *during and after surgery, with gradual tapering off to prevent this irreversible* shock As a reminder, the hormones can be given orally, intramuscularly or intravenously as necessary

Use of hydrocortisone or prednisolone TBA intra-articularly effects maximum benefit when used in the knee joints or small joints of the fingers There are some patients with rheumatoid arthritis who derive permanent benefit. However, the benefit is much greater in similar joints when they are afflicted with osteoarthritis. The technique for injection of the knees is easy if a small needle is used and introduced just below the patella, with the knee in a flexed position (e g., over the edge of the examining table). It is much less difficult than the lateral approach A satisfactory method of injection of the phalangeal joints is to select a needle as small as 26 gauge and insert it just under the capsule. No attempt is made to enter the space between articulating surfaces. This method is almost painless and does not injure the joint surfaces in any way A dose of the steroid should be injected every seven to fourteen days for four or five occasions. The knee joints respond best following the injection of 50-200 mg. of hydrocortisone or prednisolone TBA. The phalangeal joint will respond to 15 mg The relief after administration has been dramatic in many instances The reader is referred to

as it may backfire and cause the patient to lose confidence. Many patients have underlying depressing psychological factors which hinder improvement When these can be discussed frankly, with lessening of undue emotional stress, the patient's mind can be put at ease Swain has noted amazing improvement in some when unhappy home relationships are corrected Margolis presents an enlightening approach to this problem (see p 42).

Often it is not necessary to provide for a psychiatrist in consultation; the attending physician has sufficient understanding to be able to handle the problems easily if he is willing to take the time to do it. However, those patients who need orthodox psychiatric care, including shock therapy, are best handled by a psychiatrist

MANAGEMENT AND EDUCATION FOLLOWING PRELIMINARY INTENSIVE TREATMENT

Ideally, the first phase of treatment has taken place during a period of three weeks in a hospital in cooperation with the Department of Physical Therapy. It is assumed that the management has been carefully and sympathetically supervised. When it is impossible for the patient to go to the hospital, a compromise must be made, but experience has proven it is not as effective.

After discharge from the hospital, or at the end of three weeks of similar therapy, the patient continues two or three weeks at home, following a modified program, before attempting to return to full-time duties During this time the patient is permitted to have less bed rest, but follows all other phases of the previously outlined program

At the end of this period, which dates five or six weeks from the initiation of therapy, the patient is usually ready and anxious to return to work. He is then instructed to follow a program of rather stable nature, which will continue for months It is a modification of the program outlined in the hospital Among the most important of these factors are (1) bed rest, as much as possible and compatible with the daily living program. A minimum of ten hours at night is most desirable and when possible, an extra hour or two during the day The bed must contain a firm mattress (2) Adherence to the several instructions outlined by the Department of Physical Therapy (3) The weekly injection of a gold salt. Therapy is discontinued if reactions occur, but may be resumed later in smaller amounts if the reaction is a mild one (4) In those patients who are unable to receive gold salts, the weekly injection of a streptococcus hemolyticus vaccine is used. (5) Adrenocorticosteroids or ACTH are used as indicated (6) Salicylates are prescribed in liberal amounts for the relief of pain and stiffness (7) Good nutrition must be maintained by the intake of a normal, well balanced diet adjusted to body build (8) Proper chairs are recom-

is no proof that the removal of an infected focus will permanently alter the course of rheumatoid arthritis. Surgical eradication should be performed only when it would be indicated if the patient did not have arthritis. The wholesale removal of tonsils and teeth and radical surgery of nasal sinuses has long since lost favor.

The correction or *prevention of deformities* is a vital factor in treatment The ideal type of mattress and the use of pillows has been discussed previously. Attention should be given to the hands of the patient as he is lying in bed, typically with fingers outstretched and wrists extended This may result in a disabled hand. As mentioned before, the patient is instructed *early in the course of treatment that the hands should be loosely closed* with wrists slightly cocked when they are not actively in use. Excessive activity of the hands is harmful and leads only to increased deformities with loss of function.

Serial plaster splints should be applied early if flexion contracture of the knee has occurred that has not responded after ten days' rest in bed. Such splints make the patient comfortable if the procedure is instituted early, otherwise, the partially flexed knee is painful. Within twenty-four hours after the application of the first cast, the pain disappears. As extension of the knee increases, new plaster casts are applied until full extension is obtained It should be emphasized that the knee be put through its range of motion several times daily as soon as possible. This preserves function as well as muscle tone. The patient soon enjoys the cast, sleeping with it in place and keeping it under the leg most of the day. The knee is exercised best, passively and actively, following the application of heat in the Physical Therapy Department Muscle tensing training is started early. As the patient is able to carry out such procedures, they are performed several times daily *in addition to the session in physical therapy.* Traction of the legs in patients with flexed knees is no longer favored in most clinics

The *psychological* aspect of treatment is vital. First, the patient must be satisfied that a thorough examination has been performed by the physician. Also, there must be conviction that the treatment outlined is most desirable and will produce the best results. With such indoctrination, a desire is created to follow the regimen with enthusiasm and understanding, *in order to attain maximal improvement* The initial visits at the beginning of therapy are crowded with details to make certain the program is started properly, but during each subsequent visit a closer relationship develops which enables the physician to inspire confidence, giving that peace of mind essential for maximum progress It is desirable to discuss some tangible objective evidence of improvement which is favorable and encouraging at such times No commitments should be made that are not based upon anticipated results It is not wise to hazard a guess without adequate foundation

7 Hench, P S., Kendall, E C, Slocumb, C H and Polley, H F Effects of cortisone acetate and pituitary ACTH on rheumatoid arthritis, rheumatic fever and certain other conditions Arch Int Med 85 545, 1950

8 Hollander, J L Intra articular hydrocortisone in the treatment of arthritis Ann Int Med 39 735, 1953

9 ——, Brown, E J, Jr, Jessar, R A., Udell, L., Smukler, N M and Bowie, M A Hydrocortisone tertiary—butylacetate by intra-articular injection J A M A 158 476, 1955

10 Home Care in Rheumatoid Arthritis Arthritis and Rheumatism Foundation

11 Howell, D S and Ragan, C The course of rheumatoid arthritis during four years of induced hyperadrenalism (IHA) Medicine 35 83, 1956

12 Lockie, L M Treatment of rheumatoid arthritis New York J Med p 1665, 1953

13 —— and Musgroove, E Physical therapy in the treatment of arthritis New York J Med 47 851, 1947

14 —— and Norcross, B M Juvenile rheumatoid arthritis Pediatrica 2 694, 1948

15 ——, Norcross, B M and George, C W Treatment of two reactions due to gold response of thrombopenic purpura and granulocytopenia to BAL therapy J A M A 133 754, 1947

16 ——, Norcross, B M and Riordan, D J Survey twenty-five years using gold salts in the treatment of rheumatoid arthritis (In press)

17 Lowman, E W Self help devices for the arthritic Institute of Phys Med and Rehabilitation New York University Bellevue Medical Center, 1954

18 Manual for Nurses Arthritis and Related Disorders Arthritis and Rheumatism Foundation

19 Norcross, B M, Lockie, L M., Constantine, A G., Talbott, J H, and Stein, R H The effect of cortone and ACTH on the histopathologic lesions of rheumatoid arthritis Ann Int Med 36 751, 1952

20 ——, Lockie, L M and Talbott, J H Evaluation of steroids in rheumatoid arthritis New York J Med 51 1031, 1951

21 Rheumatism and Arthritis (Tenth Rheumatism Review) Review of American and English Literature of Recent Years Ann Int Med 39 499, Oct 1953 and p 758, Nov 1953

22 Rheumatism and Arthritis (Eleventh Rheumatism Review) Review of American and English Literature of Recent Years Ann Int Med 45 831, Nov 1956 and p 1059, Dec 1956

23 Primer on the Rheumatoid Diseases Am Rheumatism Assoc J A M A 152 405, 522, 1953

24 Wise, C S Physical medicine in rheumatoid arthritis Bull Rheumat Dis 7 3, Nov 1956

mended, which means the use of only occasional or straight-backed chairs. At no time is the patient allowed to sit in a lounging chair or davenport. (9) In order to remind the patient to maintain good posture, he is asked to stand with body erect and to take six deep breaths every hour on the hour. (10) It is necessary to continue psychotherapy in order to preserve the desire by the patient to follow the program. There must not be any letup in reassurance. (11) The physician as well as the patient should maintain maximum interest in the problem. Office personnel cannot take the place of the doctor at the time of an office visit by the patient suffering with arthritis

SUMMARY

The optimum management of rheumatoid arthritis consists of a well-integrated program tailored to the particular requirements of each individual patient. This can be initiated best in a three-week period of hospitalization, during which time careful supervision of the treatment and education of the patient is possible Bed rest, physical therapy, gold salt injections, analgesics, sedatives, prevention or correction of joint deformities, maintenance of optimal nutrition, use of corticosteroids or ACTH, and intensive psychotherapy are among the important phases of treatment of this stubborn disease Following indoctrination in the hospital, the patient should appreciate the fundamentals involved in treatment and be prepared to continue the therapy at home for many months if necessary, until maximum improvement is noted. With current therapy, the patient should anticipate an excellent result and look forward to the pursuit of a normal, useful life

Selected Bibliography

1 Boland, E W Prednisone and prednisolone therapy in rheumatoid arthritis J A M A *160* 613, 1956

2 Bunim, J J, Sokoloff, L, Williams, R R and Black, R L: Rheumatoid arthritis a review of recent advances in our knowledge concerning pathology, diagnosis and treatment J Chron Dis *1* 168, 1955

3 Cecil, R L, Nicholls, E E and Stainsky, W. J · The bacteriology of the blood and joints in chronic infectious arthritis. Arch Int Med *43*· 571, 1929

4 Dawson, M H, Olmstead, M and Boots, R, H · Agglutination reactions in rheumatoid arthritis I Agglutination reactions with streptococcus hemolyticus. J Immunol *23* 187, 1932

5 Freyberg, R H *Present status of gold therapy for rheumatoid arthritis.* J A M A *143* 418, 1950

6 Hench, P S, Kendall, E C, Slocumb, C H and Polley, H F · The effect of a hormone of the adrenal cortex (17 hydroxy-11-dehydrocorticosterone: Compound E) and of pituitary adrenocorticotropic hormone on rheumatoid arthritis. Preliminary report. Proc Staff Meet, Mayo Clin. *24* 181, 1949

7 Hench, P. S., Kendall, E. C., Slocumb, C H and Polley, H F Effects of cortisone acetate and pituitary ACTH on rheumatoid arthritis, rheumatic fever and certain other conditions Arch Int Med 85 545, 1950

8 Hollander, J L Intra articular hydrocortisone in the treatment of arthritis Ann Int Med 39 735, 1953.

9 ——, Brown, E J, Jr., Jessar, R A, Udell, L., Smukler, N M and Bowie, M A Hydrocortisone tertiary—butylacetate by intra-articular injection. J A M A 158 476, 1955

10 Home Care in Rheumatoid Arthritis Arthritis and Rheumatism Foundation

11 Howell, D S and Ragan, C The course of rheumatoid arthritis during four years of induced hyperadrenalism (IHA) Medicine 35 83, 1956

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15 ——, Norcross, B M and George, C W Treatment of two reactions due to gold response of thrombopenic purpura and granulocytopenia to BAL therapy J A M A 133 754, 1947

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20 ——, Lockie, L M and Talbott, J H Evaluation of steroids in rheumatoid arthritis New York J Med 51 1031, 1951

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22 Rheumatism and Arthritis (Eleventh Rheumatism Review) Review of American and English Literature of Recent Years Ann Int Med 45 831, Nov 1956 and p 1059, Dec 1956

23 Primer on the Rheumatoid Diseases Am Rheumatism Assoc J A M A 152 405, 522, 1953

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Adrenal Cortical Steroids and Some of Their Synthetic Analogues in the Treatment of Rheumatoid Arthritis

by Edward W. Boland

EIGHT YEARS HAVE PASSED since it was discovered that the inflammatory reaction and certain biochemical abnormalities of rheumatoid arthritis may be reduced rapidly by the administration of cortisone and corticotropin. During this period the relation of adrenal cortical steroids to the disease has been the subject of intensive inquiry. Investigation with the hormones has proceeded mainly in three directions: (1) their use as research tools to explore the complex and poorly understood pathophysiologic mechanisms of the disease; (2) their direct application as treatment agents; and (3) the production of new synthetic steroid derivatives which, it is to be hoped, might possess higher therapeutic indices than the naturally occurring hormones Developments have taken place rapidly, and it is understandable that as experience and knowledge have accrued, opinions regarding the therapeutic utility of steroids have changed accordingly. An attempt will be made herein to discuss briefly the present position of adrenal cortical hormones and some of their analogues in the practical management of rheumatoid arthritis.

GENERAL CONSIDERATIONS

Despite the vast amount of basic research that has been accomplished, the physiologic mechanisms involved in the suppression of inflammatory processes by adrenal cortical hormones are still not understood. Some investigators believe that rheumatoid arthritis and its related collagen disorders may represent hypersensitivity reactions of connective tissue, and that the antiphlogistic steroids or their metabolites, operating at the tissue level, inhibit the excessive reactivity Whether their influence is exerted by interfering with antigen-antibody mechanisms, by blocking tissue enzyme systems, by modifying cellular permeability, or by counteracting a "mineralocorticoid type of response" are theoretical considerations, none of which is convincingly supported by experimental evidence.

The adrenal glands of patients with rheumatoid arthritis appear anatomically normal when they are examined by usual histologic techniques However, certain laboratory and clinical observations suggest that a relative

functional insufficiency may exist during active phases of the disease. Satisfactory reversal of the pathologic changes is not promoted by cortical steroids unless they are supplied in supernormal amounts, a feat which, under the circumstances of the disease, the patient's own adrenal glands fail to achieve. Whether this represents an inordinate demand of diseased tissues for steroid in the presence of normally functioning glands, inadequate cortical function (due to insufficient anterior pituitary stimulus or to depressed adrenal cortical activity), or a derangement of steroid metabolism is not known. Recent investigations have shown that the diurnal pattern for the excretion of steroid metabolites in the urine and for the levels of hydrocortisone in the plasma is abnormal among patients with active rheumatoid arthritis. Excretion rates and plasma levels tend to be low, especially in the early morning hours. The significance of these observations has not been fully evaluated, but attempts have been made to correlate the lowered steroid levels with symptoms of morning stiffness, so characteristic of the disease.

A number of practical considerations are germane in the therapeutic application of antirheumatic steroids. (1) Their influence is not specific against any one disease or group of diseases. Inflammatory or hypersensitivity reactions provoked by various irritants may be reduced by their administration. Any specificity they possess is against some yet unidentified factor common to a number of disease states. (2) They do not destroy pathogenic organisms or directly antagonize toxins, allergens, or other noxious agents. Rather, their benefits seem to be achieved through a modification of tissue responses to adverse stimuli. (3) Their action is not curative, but in responsive self limited conditions they may restrain pathologic processes while the disease runs its course or undergoes remission. (4) Most of their effects, favorable and unfavorable, are temporary. In chronic maladies such as rheumatoid arthritis, the maintenance of therapeutic benefits is dependent on their more or less continuous administration. (5) Even with continued treatment, successful control of the rheumatic manifestations may not be preserved indefinitely, because some patients apparently become relatively refractory to the drugs after they have been used for extended periods. (6) Steroid therapy frequently fails to halt progression of the rheumatic process even while symptomatic relief is being maintained. (7) Each of the presently available anti inflammatory steroids promotes, in addition to its antirheumatic effect, a variety of other physiologic actions. Many of these are undesirable, producing unwanted side effects and sometimes dangerous complications, and they serve as obstacles to successful management. (8) A number of pathologic conditions may be aggravated by steroid administration; when these coexist in a rheumatoid patient, they set up relative or

absolute contraindications for treatment. (9) The prolonged administration of steroids produces functional depression of the patient's adrenal cortices; although reversible, this creates a potential hazard that requires the application of special protective measures during periods of extraordinary stress.

INDICATIONS FOR STEROID THERAPY AND SELECTION OF PATIENTS

From the preceding considerations it is obvious that the adrenal cortical hormones have many shortcomings as suppressive agents for rheumatoid arthritis. But they also have distinct attributes and they constitute the only therapeutic weapons now available that have the capacity to inhibit rapidly the signs and symptoms of the disease. When properly prescribed, they allow rehabilitation for useful occupation in a high percentage of patients, indeed, the rheumatic manifestations of many patients defy successful control by other existing means. Despite prevalent, justifiable criticisms of their inadequacies, most rheumatologists would bewail the prospect of managing many of their rheumatoid patients without the accessibility of steroid compounds.

Authorities agree that steroid therapy should be restricted for carefully selected cases and that it should not be prescribed to the exclusion of other time-tested helpful procedures. Management should also include a sound comprehensive program consisting of well-regulated rest and exercise, properly balanced diet, avoidance of undue emotional stress, physiotherapeutic procedures and graded muscle exercises, careful handling of affected joints with proper supports and splints, occupational and rehabilitative measures, and simple analgesics. Steroid administration does not prohibit the use of gold salts Apparently the two forms of treatment may be employed together at times with advantage

The author's present attitude toward the selection of patients for steroid therapy may be summarized as follows (1) More conservative and simpler methods should first be given a fair trial This applies particularly to patients whose disability is not great, whose disease is relatively mild in form or short in duration—when judgment based on experience indicates that the process has a good chance for early natural reversal If conservative measures fail or prove inadequate, the patient's suitability for steroid therapy should be examined (2) Candidates should qualify on several points of stability: capacity for sustained cooperation during the necessarily prolonged period of treatment, full understanding of the limitations and possible hazards involved, willingness to accept partial improvement from doses of reasonable size—to compromise, if necessary, for "part of a loaf" in the interest of safety, and availability for close medical supervision. (3) Steroids should be prescribed only when the rheumatoid process is potentially responsive. Improvement may be expected in those manifestations due to active inflammation, not in those due to irreversible structural damage. (4) Absolute con-

traindications must be ruled out before instituting treatment These include active tuberculosis, psychoses and severe psychoneuroses, severe diabetes mellitus, active peptic ulcer, marked renal insufficiency from any cause, and Cushing's syndrome (5) Relative contraindications should be weighed carefully. The risk of administering steroids is increased by certain conditions, i e, arrested tuberculosis, active infections, cardiovascular or renal disease, diabetes mellitus of any degree, past history of peptic ulcer, tendency to thromboembolic phenomena, generalized osteoporosis, convulsive disorders, and pregnancy.

PREPARATIONS AND THEIR COMPARISONS

Several anti-inflammatory steroid preparations are commercially available In general, they promote qualitatively similar antirheumatic responses and they all share the major limitations of steroid therapy However, some differ significantly in milligram potency, in certain metabolic properties which influence the development of complicating side effects, and in their relative effectiveness on systemic and intra articular administration These variances are sufficient to demand discriminate choice of preparations for individual patients.

Cortisone and Hydrocortisone Both hormones may be isolated in crystalline form from adrenal cortical extracts, but it is probable that hydrocortisone is the principal glucocorticoid which is secreted naturally. The compounds bear close chemical resemblance, their structural formulae differing in but one detail hydrocortisone has a hydroxyl radical where cortisone has a ketone group at the 11th carbon position in the steroid nucleus (fig 1). The metabolic and antirheumatic activities of the two hormones correspond qualitatively, but quantitatively hydrocortisone has greater milligram potency (estimated to be twice as great from biologic tests in animals and 25 to 50 per cent greater from clinical comparisons), accordingly, smaller milligram doses of hydrocortisone are required to promote equivalent clinical improvement Some investigators hold that hydrocortisone exhibits some therapeutic superiority; when smaller but equally efficient milligram doses are employed orally, certain side effects (psychic stimulation, salt and water retention, excessive appetite, and weight gain) have seemed to be fewer or less pronounced

Hydrocortisone is supplied for oral use in its nonesterified form (free alcohol) and for intra articular injection as an ester (acetate or tertiary-butyl acetate). The esterified preparations are less soluble and are poorly absorbed, this lowers their efficiency orally but prolongs their local action The strengths of cortisone (free alcohol) and cortisone acetate are similar on oral administration, and as the acetate ester is easier to manufacture, it is provided commercially Results from intra articular instillations of cortisone prepara-

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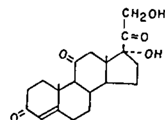
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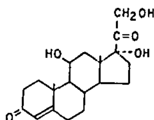
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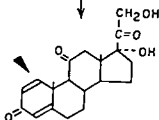
tions are unreliable and distinctly inferior to those obtained from esters of hydrocortisone.



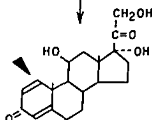
CORTISONE



HYDROCORTISONE



PREDNISONE
(Δ^1-cortisone)



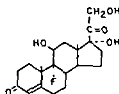
PREDNISOLONE
(Δ^1-hydrocortisone)

Prednisone and Prednisolone These compounds are synthetic analogues of cortisone and hydrocortisone, *respectively. They differ chemically from the* parent hormones by the addition of a double bond between the first and second carbon positions in the steroid nucleus (fig. 1). Prednisone and prednisolone exhibit similar milligram potency and metabolic activity on systemic administration, for practical purposes they are interchangeable. Their antirheumatic power per milligram (as gauged by clinical comparisons) and their adrenocortical activity (as measured by assays in animals) are approximately four times greater than those of hydrocortisone. In other words, the degree of improvement in rheumatoid manifestations obtained by a given amount of hydrocortisone would be sustained by one fourth the dose, in milligrams, of prednisone or prednisolone (as an average). Given orally in dosages of equal antirheumatic strength, prednisone and prednisolone demonstrate the same metabolic properties as cortisone and hydrocortisone with the following exceptions: (1) Their tendency to produce salt and water retention, potassium loss, and blood pressure elevation is distinctly less; this

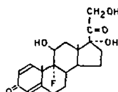
dissociation of properties is often useful clinically, allowing some patients to take proportionately larger and clinically more effective antirheumatic doses (2) They are more prone to cause gastric irritation and peptic ulcers, ecchymotic skin lesions, and vasomotor symptoms.

Esters of prednisolone (acetate, tertiary-butyl acetate, etc) are effective on intra-articular instillation and demonstrate greater milligram potency than corresponding esters of hydrocortisone Prednisone preparations, like those of the cortisone parent, exert an indifferent local response

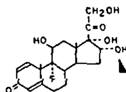
New Experimental Synthetic Steroid Analogues (fig. 2). The steroid nucleus lends itself to almost countless permutations in structure, and during the past few years chemists have devised hundreds of new synthetic analogues of cortisone and hydrocortisone Studies with these substances have provided much information regarding the relation of the structural configuration of steroids to their biologic actions, and hope prevails that compounds with more selective antirheumatic activity will be devised in the future. It now appears that the steroid molecule must have oxygen groupings at the 11th and 17th carbon positions in order to exert anti-inflammatory effects, but certain changes elsewhere may materially influence not only anti-inflammatory potency but certain accessory physiologic properties A few recent developments, though still in the investigative stage or not directly applicable to the treatment of rheumatic diseases, are worthy of mention, as they may foreshadow the creation of new drugs to be placed at the physician's disposal.



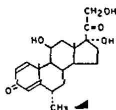
9α-FLUORO-HYDROCORTISONE



9α FLUORO-PREDNISOLONE



9α-FLUORO-16α-HYDROXY-PREDNISOLONE



6α-METHYL-PREDNISOLONE

Two discoveries seem to have particular significance: (1) The demonstration that halogen atoms placed at the 9th carbon position greatly increase the biologic power of hydrocortisone. One such compound, 9-alpha fluorohydrocortisone, for example, has antirheumatic activity which is ten times greater than its kindred compound. Its salt-retaining and potassium-losing properties, however, are increased even to a greater extent and this has precluded its use as an antirheumatic agent. (2) The discovery that the placement of a double bond between the first and second carbon atoms of cortisone and hydrocortisone, yielding prednisone and prednisolone, increases the anti-inflammatory strength of the parent compounds without augmenting electrolyte activity. Subsequently it was logical for chemists to combine these two structural changes. By so doing the biologic activity of the compounds created was found to be multiplicative. Nine-alpha fluoroprednisolone, for example, has been determined to be 40 times as potent in antirheumatic strength as hydrocortisone; but, again, this compound has tremendously powerful sodium-retaining and potassium-losing activity and could not be applied as an antirheumatic drug. Later it was demonstrated that the placing of a hydroxyl group at the 16-alpha position attenuates the excessive electrolytic effect, without eliminating the anti-inflammatory action, of 9-alpha fluoroprednisolone This has led to the development of a new series of compounds, one of which (9-alpha fluoro-16-alpha hydroxy prednisolone-triamcinolone) is currently undergoing clinical trial.

Recently, it was discovered also that the addition of a methyl group at the second carbon position selectively enhances the sodium-retaining and potassium-wasting properties of 11-oxygenated corticosteroids. But if the methyl radical is introduced at the 6th carbon position instead, no such increase in electrolyte activity results. One of these compounds, 6-methyl prednisolone, has been found to exhibit powerful glycogenic and anti-inflammatory activity in animals, and it is now being evaluated in rheumatoid pa-

[illegible]

chemical innovations to come.

DOSAGE PRINCIPLES AND PLANS FOR SYSTEMIC ADMINISTRATION

Various treatment programs have been tried, but the prolonged uninterrupted plan of administration, using minimal maintenance doses, has proved most practical. With this scheme, dosage regulation is usually accomplished in three stages (1) an initial period of suppressive doses; (2) a period of gradual dose reduction, and (3) the period of continuous administration with minimal maintenance doses.

Some General Principles The basic policy should be to promote and sustain a degree of disease suppression which is optimal for the individual

patient, i e , to provide that improvement of the rheumatic manifestations and functional capacity that may be accomplished with dosages which, on long-term administration, are consistent with the avoidance of significant hormonal complications Complete inhibition of the disease should not be sought—rather, both the patient and the physician must be satisfied with the improvement which may be achieved with "safe" levels of dosage In general, clinical improvement of 75 to 85 per cent of the pretreatment status should be considered as satisfactory even for patients receiving well tolerated doses. Since rheumatic patients differ in their response to steroids, in their susceptibility to untoward reactions, and in the circumstances which attend their illness, there can be no fixed rules for therapy However, the following lessons gained from experience may serve as helpful guides

(1) Satisfactory degrees of improvement cannot be expected for all patients. Many, especially those with severe or very active disease whose dosage requirements for good control are greater than can be tolerated, may have to settle for results which, even though still worthwhile, are less than desired

(2) Initial doses should not be too large or continued too long The achievement of rheumatic control in a leisurely fashion, with dosages closer to the estimated maintenance level, will often prevent unwanted reactions from the beginning It is better to avoid the drama from early "overcharging" than to struggle with complications thereafter

(3) Reductions from initial suppressive to smaller maintenance doses should be made slowly by small decrements A sudden drop in dosage may result in loss of clinical control

(4) Maintenance requirements vary in individual cases, but the amounts needed depend more on the activity of the process and on the physical or emotional stress to which the patient is subjected than on other factors Successful management may depend as much on proper regulation of the patient's activities as on proper manipulation of his medication.

(5) Once maintenance doses are established they should be considered as relative, not fixed Fluctuations in disease activity are characteristic of rheumatoid arthritis and demand adjustments in dosage These adjustments should be made by small milligram changes, rather than by large or erratic swings in dosage.

(6) The size of the maintenance dose should be determined principally on the basis of clinical improvement and the occurrence of undesirable side effects. The erythrocyte sedimentation rate and other laboratory tests are not dependable gauges

(7) With oral therapy steroids should be prescribed in divided doses because available preparations are absorbed quickly and their effects are dissipated rapidly. Proper division of dosage, such as 3 or 4 times a day

(following meals and at bedtime) provides more even control and minimizes the total daily requirement. *A relatively larger divided* dose *taken in the* morning when symptoms are worse may be advantageous.

(8) Some patients who have been well controlled for prolonged periods may eventually become relatively refractory; improvement may deteriorate despite increasing and finally prohibitive amounts of steroid. In such instances responsiveness may return if the drug is gradually withdrawn and a treatment-free period of 2 to 3 months is allowed.

(9) When, for any reason, steroid therapy is discontinued, the dosage should be tapered off slowly to prevent withdrawal symptoms (weakness, fatigue, lowered resistance to stress, sudden flare-up of articular manifestations, etc) Generally it is best to gradually wean the patient from treatment *over a period of 2 to 3 months*

Initial Doses. Optimal doses at the beginning vary among individual patients, but the amount depends mainly on the severity of the rheumatoid arthritis. As a rule, total daily doses in the neighborhood of the following suffice severe cases—60 to 70 mg. for hydrocortisone, 12.5 to 17 5 mg for prednisone and prednisolone, moderately severe cases—50 to 60 mg for hydrocortisone, 10 to 12.5 mg. for prednisone and prednisolone, moderate *cases—40 to 50 mg for hydrocortisone, 7 5 to 10 mg for prednisone and* prednisolone These amounts should be continued until satisfactory suppression of the active clinical manifestations has resulted, ordinarily for 2 to 4 weeks. Usually steroid therapy should be denied to patients with mild disease

Reduction of Dose Dosage should be gradually lowered in step-like fashion, reductions of 5 to 10 mg with hydrocortisone and 1 25 or 2 5 mg of prednisone and prednisolone being made at intervals of every 7 to 14 days, sometimes more slowly The smallest total daily amount which will control the manifestations adequately and/or safely should be considered as the maintenance dose.

Maintenance Dose Among our patients maintenance doses per day for *hydrocortisone have usually ranged from* 40 *to* 60 *mg* in severe cases, 30 to 50 mg in moderately severe, and 15 to 30 mg. in moderate cases. Doses for prednisone and prednisolone have ranged from 10 to 15 mg. for severe cases. 5 to 15 mg. for moderately severe, and 2 5 to 7 5 for moderate cases Once established, maintenance therapy should be *continued without interruption*, the doses being adjusted from time to time to accommodate shifts in disease activity or to control adverse reactions As the frequency and severity of unwanted side effects are directly related to the amount of steroid used, dosages must not exceed those which can be *well tolerated—but in* practice it is necessary to view minor Cushingoid signs as acceptable nuisances and not obligatory reasons for lowering dosage Our experience would indicate that the following doses constitute the upper limits which can be

prescribed safely over long periods: for men—60 to 70 mg a day of hydrocortisone, 15 to 17.5 mg. a day of prednisone or prednisolone, for women—40 to 50 mg a day of hydrocortisone, 10 to 12.5 mg a day of prednisone or prednisolone.

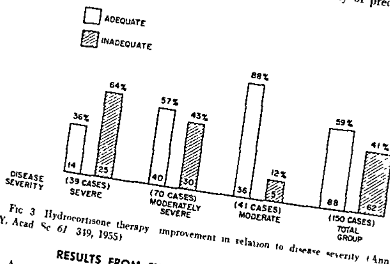


Fig 3 Hydrocortisone therapy improvement in relation to disease severity (Ann N Y. Acad Sc 61 349, 1955)

RESULTS FROM SYSTEMIC STEROID THERAPY

An attempt will be made to summarize the results of long-term steroid therapy from statistical data drawn from two recent studies The first involved 150 rheumatoid arthritic patients treated with hydrocortisone and observed for continuous periods of from 9 to 36 months The second was comprised of 141 patients treated with prednisone or prednisolone for continuous periods of from 6 to 9 months

Over-all Results from Prolonged Hydrocortisone Therapy Among 150 patients treated with hydrocortisone, improvement at the time of analysis was judged to be adequate or satisfactory in 59 per cent of the patients, and less than satisfactory in 41 per cent (fig 3) Inadequate degrees of improvement were noted in 62 patients for one or more reasons 37 (62 per cent) failed to respond satisfactorily to reasonably sized doses from the beginning of treatment, 13 (22 per cent) were controlled well at first but later became relatively unresponsive to the hormone, 37 (62 per cent) developed hormonal side reactions which prohibited the use of sufficiently effective doses, and 5 (8 per cent) presented miscellaneous other reasons for limited improvement. Female patients fared about as well as male patients; inadequate improvement was recorded in 42 per cent of the former and 39 per cent of the latter.

Factors Influencing the Success of Hydrocortisone Therapy Aside from the recognized correctible mistakes in management (i e., poor selection of patients, inadequate supervision, improper dosage regulation, neglect of appropriate rest and simple complemental measures, avoidance of trauma, etc.), which may lead to failure, therapeutic results are conditioned chiefly by two factors—the severity or activity of the disease and the duration of the arthritis prior to treatment

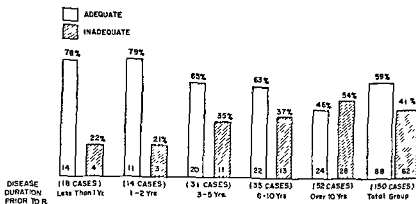


FIG 4 Hydrocortisone therapy improvement in relation to disease duration (Ann N Y. Acad Sc *61*: 349, 1955)

At the time of analysis, improvement was graded as adequate in 36 per cent of the patients with severe, 57 per cent of patients with moderately severe, and 88 per cent of patients with moderate disease (fig. 3). For satisfactory control the more severe cases all too often required excessive doses—doses which could not be tolerated or which were considered unsafe for long-term administration. Doubtless, over-all statistical results would be more favorable in any series containing a higher percentage of moderate and some mild cases The remission rate was greater in patients with moderate disease (14 5 per cent) than in those whose arthritis was moderately severe (7 1 per cent) or severe (0 025 per cent).

Percentagewise, results were most favorable when the arthritis was of relatively recent origin. The crucial point was approximately two years, and thereafter, as disease durations lengthened, the proportion of adequate responses lessened progressively (fig. 4) The remission rate was decidedly lower in patients whose disease had been established more than two years (4 per cent) than when the duration was two years or less (22 per cent).

Deterioration of Improvement with Prolongation of Hydrocortisone Therapy. Analyses made at intervals during the period of observation revealed that as treatment was continued over the months, the number of pa-

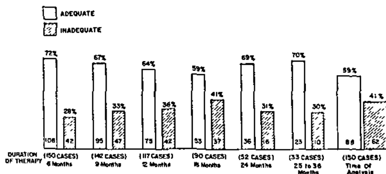


FIG 5 Hydrocortisone therapy improvement in relation to duration of treatment (Ann N Y Acad Sc 61 349, 1955)

tients showing adequate improvement became smaller The data summarized in figure 5 may be confusing unless it is understood that patients were added to the series as the study progressed and that others were dropped from time to time because of remission, insufficient benefit, or other reasons. The disease was satisfactorily restrained in 72 per cent of patients at the end of 6 months, but this percentage declined to 59 per cent at 18 months.

Influence of Long-Term Hydrocortisone Therapy on Disease Progress Among the 150 patients, 50 of them (or 33 per cent) showed evidence of disease progression during the observation period Functional capacity was not modified significantly by advancement of the arthritis in 19 of the patients, but it declined in the remaining 31 As might be anticipated, the ability of steroid therapy to restrain progress of the disease varied indirectly with the severity or activity of the rheumatoid arthritis Progression was

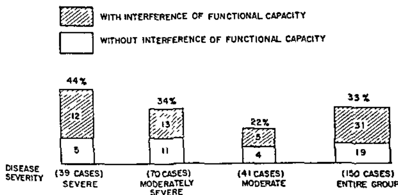


FIG 6 Hydrocortisone therapy disease progression in relation to disease severity (Ann N Y Acad Sc 61 349, 1955)

noted in 44 per cent of severe cases, 34 per cent of moderately severe cases, and in 22 per cent of moderate cases (fig. 6). There was no uniform correlation, however, between the frequency of disease progression and the duration of the arthritis prior to therapy (fig. 7).

Comparison of Over-all Results from Hydrocortisone, Prednisone and Prednisolone Results from relatively long-term studies with the three com-

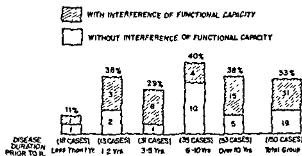


FIG 7 Hydrocortisone therapy disease progression in relation to disease duration (Ann N Y Acad Sc *61* 349, 1955)

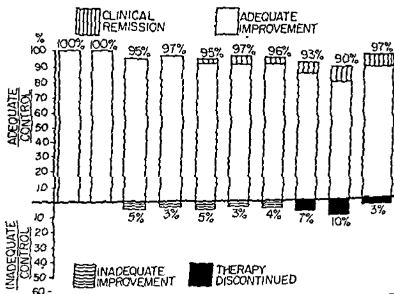


FIG 8 Clinical improvement in patients receiving prednisone or prednisolone as initial therapy (J A M A *160* 613, 1956).

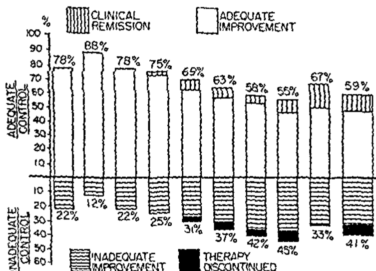


FIG 9 Clinical improvement after transfer of medication to prednisone or prednisolone in patients adequately controlled with hydrocortisone (J A M A 160 613, 1956)

pounds differed little in patients who were treated with steroids for the first time. In 32 patients who received prednisone or prednisolone as initial therapy, the percentage showing adequate degrees of improvement at the time of analysis was almost identical to that recorded for a group of similar composition treated initially with hydrocortisone (fig. 8)

That prednisone and prednisolone are capable of maintaining satisfactory response among patients amenable to hydrocortisone therapy was evident in 39 of our patients whose treatment was transferred while they were being maintained successfully on hydrocortisone (fig 9). The doses employed for prednisone and prednisolone were, on an average, approximately one-fourth as large in milligrams as for hydrocortisone Six to 9 months after transfer of treatment, 38 of the 39 patients had retained an adequate treatment status

Our observations, like those of others, demonstrated that replacement of therapy with prednisone and prednisolone may restore adequate levels of improvement in a significant number of patients whose arthritis has escaped control after the prolonged administration of hydrocortisone. Seventy of our patients whose improvement had deteriorated below adequate levels were

transferred to prednisone or prednisolone. In general, this was a stubborn group of patients, most of whom had severe or moderately severe diseases (96 per cent) for long duration (over 3 years in 82 per cent). They had received hydrocortisone therapy uninterruptedly for long periods (average 19 *months*) and in amounts which were judged in individual cases as upper limits with respect for safety. The doses employed for prednisone or *prednisolone* were larger in terms of antirheumatic strength (average 5.2 mg per day greater than the calculated equipotent dose of hydrocortisone, an *amount* which would be roughly equivalent to an extra 20 mg. a day of hydrocortisone). Following change of treatment to the derivatives, the *immediate* results were favorable in 58 of the 70 patients. As therapy was continued, the number of patients showing adequate improvement gradually diminished, but at the end of 6 to 9 months, rheumatic control remained satisfactory in 47 per cent (fig. 10). Considering the composition of the group, the restoration and maintenance of major improvement in nearly one half of the patients for 6 to 9 months was an impressive accomplishment—and, although statistics are not available, successful management has now continued in many for as long as two and one-half years.

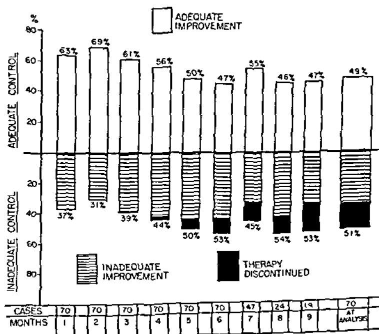


Fig. 10 Clinical improvement after transfer of medication to prednisone or prednisolone in patients *not* adequately controlled on hydrocortisone (J.A.M.A. *160* 613, 1956).

Comparison of Unwanted Side Effects from Prednisone, Prednisolone, and Hydrocortisone; Their Influence on Management Observations regarding the incidence and character of hormonal side reactions and complications from these three steroids permit the following deductions: (1) The total incidence for side effects is not lowered when prednisone or prednisolone is substituted for hydrocortisone in smaller, but equally potent, antirheumatic doses; (2) the total number of side effects is increased when prednisone and prednisolone are employed in dosages which exceed equivalently potent amounts of hydrocortisone, (3) prednisone and prednisolone differ from hydrocortisone in their tendency to produce certain individual undesired reactions

A comparison of the incidence of individual side effects noted during

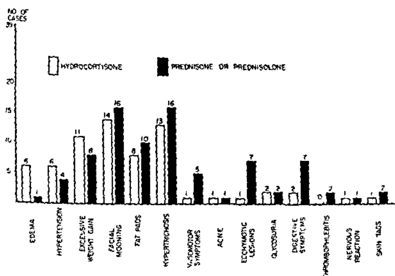


FIG 11 Number of individual adverse effects among 39 patients on hydrocortisone therapy compared with number following transfer of medication to prednisone or prednisolone in dosages of approximately equivalent antirheumatic potency (J A M A *160* 613, 1956)

hydrocortisone therapy and after 6 to 9 months of prednisone or prednisolone therapy given in doses that were smaller in terms of milligrams, but approximately equal in antirheumatic potency, is shown in fig 11. The figures indicate that prednisone and prednisolone have a lessened tendency for salt and water retention and for blood pressure elevation, but a greater proclivity for digestive complaints, ecchymotic skin lesions, and vasomotor symptoms.

Their disposition for other reactions differs little from that of hydrocortisone.

The differences in tendency to promote individual untoward signs are demonstrated more prominently among patients whose treatment was transferred from hydrocortisone to prednisone or prednisolone in dosages which exceeded those of equal potency (fig. 12). Even with proportionately higher doses, the incidences of fluid retention and blood pressure elevation were distinctively reduced with the synthetic analogues; but again, the number of patients with digestive symptoms, purpuric lesions, and hot flushes increased sharply.

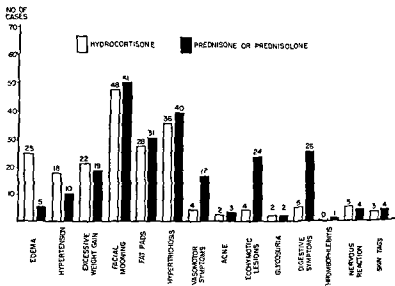


FIG. 12 Number of individual adverse effects among 70 patients on hydrocortisone therapy compared with number following transfer of medication to prednisone or prednisolone in dosages which, in terms of antirheumatic potency, were greater than with hydrocortisone (*J.A.M.A. 160* 613, *1956*)

The disparity in incidence for two reactions, electrolyte disturbances and digestive complications, deserves special comment. The lowered salt and water retaining activity of prednisone and prednisolone often permits the application of more potent and effective dosages, especially when edema from hydrocortisone or cortisone is the deterring factor in management. This, together with correction of hypertensive reaction (which may be related) in others, is responsible, at least in part, for the improved status which may result from change of medication in patients whose clinical control has deteriorated after prolonged hydrocortisone or cortisone therapy. On the other hand, the greater frequency of digestive symptoms and complications with

prednisone and prednisolone is disconcerting. Among 109 of our patients who were subjected to transfer of treatment, symptoms characteristic of ulcer or less definite complaints (postcibal nausea, gaseous dyspepsia, etc) were noted in 7 during hydrocortisone administration, and in 33 after the substitution of prednisone or prednisolone Gastrointestinal x-ray studies were accomplished in the 33 symptomatic patients, and peptic ulcers were demonstrated in 8 of them (gastric in 4, duodenal in 4). 3 were complicated by gross hemorrhage, none by perforation In each instance the roentgenographically demonstrable ulcers healed with rigid ulcer management, including the use of anticholinergic drugs, prednisone or prednisolone administration was discontinued in 3 but not in the other 5 patients.

Eventually all patients receiving prednisone or prednisolone were advised to avoid highly-seasoned and irritating foods and to take non-absorbable antacids (aluminum hydroxide gel with magnesium trisilicate) with each divided dose of steroid as prophylactic measures, interval feedings of bland food or milk were prescribed for some These procedures lessened the freqeuncy of digestive complaints decidedly, but it was not evident whether they actually prevented the development of peptic ulcers. In an attempt to clarify this point, 151 of our patients were recently subjected to routine gastrointestinal x ray studies Each of the patients had received prednisone or prednisolone uninterruptedly for 6 to 18 months, and for 6 or more months antacids had been taken regularly with each dose of steroid Despite this measure, 9 active peptic ulcers were discovered, 6 of which were prepyloric in location and 3 were duodenal. The defects were accompanied by characteristic ulcer symptoms in 6 patients, but 3 were totally asymptomatic How many ulcers may have been prevented by complemental antacids cannot, of course, be answered—but it is clear that they frequently fail to protect against the complication

PREFERENCE OF AVAILABLE STEROIDS FOR SYSTEMIC THERAPY

It would appear that each of the steroids effective against rheumatoid arthritis has a place among our therapeutic resources and that they should complement, rather than compete with, each other On the basis of statistical results of long-term administration, there would seem to be little to choose among hydrocortisone, prednisone and prednisolone as initial treatment agents Prednisone or prednisolone appears to be the drug of choice when salt and water retention is an actual or potential problem (congestive heart disease, arterial hypertension, edema from cortisone or hydrocortisone administration, etc) and in patients whose response to the older steroid proves to be inadequate. Conversely, hydrocortisone should be preferred in patients with past history of peptic ulcer, gastric irritation from the new steroids, and perhaps under other circumstances not yet defined

SOME NOTES ON THE ACCEPTABILITY, PREVENTION, AND CONTROL OF UNWANTED SIDE EFFECTS

The various risks implicit in the therapeutic use of steroids have now been fairly well determined. Most undesirable reactions are fully reversible and disappear promptly or fairly promptly with reduction of dosage or cessation of administration Nevertheless, their intrusion serves as a primary obstacle to the more successful application of steroids. Indeed, the achievement of satisfactory results is often a matter of striking an effectual balance, through dosage regulation and adjunctive measures, between wanted and unwanted steroidal effects But the attainment of this balance is not always possible and not infrequently good rheumatic control must be sacrificed in order to curb accessory manifestations of the drugs

Generalized obesity and abnormal deposits of adipose tissue in the cheeks (facial mooning), supraclavicular fossae, and the back of the neck are *among the most common signs of steroid excess Weight gain is more* easily prevented than corrected, and it is advisable to limit the caloric intake during treatment as soon as the patient's weight approaches an optimal level *Localized deposits of fat decrease or disappear with dose reduction but minor* changes. such as slight or moderate facial mooning, may be safely accepted by the patient if lowering of dosage seriously interferes with symptomatic relief.

All anti-inflammatory steroids produced so far have glycogenic activity, but apparently non-diabetic patients have sufficient functional reserve of islet tissue to offset their anti-insulin effects at ordinary levels of dosage. The sugar metabolism of patients with diabetes mellitus may be greatly disturbed by steroid administration, and frank diabetes requiring more than minimal amounts of insulin for control is usually a contraindication to treatment. Mild or latent diabetes need not necessarily prohibit their use in moderate doses, providing the aggravated condition can be handled by dietary restriction and insulin if necessary. Prednisone, prednisolone, and hydrocortisone create about the same degree of disturbance in carbohydrate metabolism when they are prescribed in equally potent antirheumatic doses

Large doses of corticosteroids may cause negative nitrogen balance. Diets high in protein and the complemental use of methyltestosterone and potassium salts have been suggested as measures to circumvent this tendency But with ordinary therapeutic doses, even though continued for long periods, clinical evidence of accelerated protein catabolism is rarely noted, and these *precautionary steps are seldom necessary*. Furthermore, our experience with uninterrupted therapy among juvenile rheumatoid arthritic patients suggests that there is little, if any, interference with growth and development when *reasonable doses are applied*

Excessive amounts of corticosteroids may impede the formation of

granulation tissue and hinder wound healing The inhibiting effect appears to be proportional to the degree of hyperadrenalism induced and little or no retardation is noted when cortisone in doses of 100 mg. a day or less, hydrocortisone in doses of 75 mg a day or less, or prednisone and prednisolone in doses of 17.5 mg. a day or less is given. In our experience postoperative wound healing has not been a problem with recommended therapeutic doses.

The occurrence of edema, usually mild but sometimes pronounced, not infrequently accompanies the use of cortisone and hydrocortisone Ordinarily this responds to dose reduction and the dietary restriction of sodium, but occasionally diuretics are required to hasten diuresis. Instances of potassium depletion from large doses of the hormones, with attendant manifestations

coupled with salt and water retention, could be hazardous to patients with impaired cardiac function As electrolyte disturbances rarely result from prednisone and prednisolone when they are given in customary amounts, the intake of salt need not be curtailed unless evidences of fluid retention appear.

Skeletal demineralization is encouraged by protracted corticosteroid therapy. Fractures, especially compression fractures of vertebral bodies resulting from minor injury or occurring spontaneously, represent serious complications They are more prone to develop when other factors conducive to osteoporosis coexist, such as senility and the presence of severe rheumatoid disease. For prophylaxis against accelerated decalcification among older persons receiving steroids, high protein and calcium diets and methyltestosterone or analogues with more selective anabolic properties (norethandrolone) have been recommended, as yet there is no firm clinical evidence of their countervailing action.

Cutaneous changes attributed to androgen activity may appear during treatment. Acne is uncommon and rarely severe Hypertrichosis is not uncommon among women and may increase gradually with prolongation of therapy. Occasionally it becomes cosmetically objectionable and a few of our patients have had the excess hair removed by electrolysis. Oligomenorrhea or amenorrhea occurs infrequently Vasomotor symptoms, such as hot flushes in menopausal women, may be aggravated, especially from prednisone and prednisolone; usually these can be controlled with oral estrogens Purpuric skin lesions are common, particularly during prednisone or prednisolone administration, neither the physiologic mechanism of their production nor methods for their correction have been found

Major mental disturbances with frank psychotic reactions have been reported in a few patients during steroid administration Most of these pa-

tients have had histories of overt psychotic episodes or of marginal psychologic adjustment, but apparently some have had no such background, the episode developing without warning and as a surprise to the physician. No serious mental reactions have been encountered in our practice. This may be owing, in part at least, to the fact that the drugs have been denied to patients with evident emotional instability or past psychotic episodes and to the fact that treatment has not been given except on a reasonable dosage basis.

The problem of gastric irritation and the development of peptic ulcers has already received comment. It is now our routine practice to invoke precautionary measures during prednisone or prednisolone administration. These include the dietary restriction of irritating foods, ingestion of the drugs following meals or food, and the concomitant administration of antacids with each divided dose of steroid While helpful, these measures unfortunately have not proved sufficiently efficacious to afford full protection.

Because corticosteroids modify local tissue reactions and the systemic responses to infectious agents, bacterial products, and miscellaneous inflammatory incitants, the signs and symptoms of unanticipated complications may be obscured to some degree. While the clinical picture of intruding diseases might be seriously veiled during the administration of large doses of steroids, complications of various kinds usually are readily recognizable when smaller maintenance doses are used. Nevertheless, physicians should be mindful that the drugs are capable of masking the usual manifestations of intercurrent diseases

The relative adrenal insufficiency that occurs during treatment has an important bearing on the patient's ability to cope with special stresses, such as trauma, severe infections, or surgical procedures. Because the patient's own adrenal glands may be unable to supply the additional corticoids demanded under such circumstances, increased amounts should be supplied exogenously. It is our practice, for example, to fortify the patient with additional steroids (usually 100 to 150 mg. of cortisone acetate intramuscularly) on the day preceding surgery and on the morning of operation; thereafter the preoperative dosage is relied upon or extra amounts are gradually tapered off, depending on the patient's condition. Hydrocortisone, suitable for intravenous administration, is kept readily available to combat sudden shock in the event that these measures prove inadequate. It is mandatory that patients established on anti-inflammatory steroids do not have their medication withdrawn at the time of surgical treatment or similar crisis.

INTRA-ARTICULAR STEROID THERAPY

Intra-articular instillations of esterified preparations of hydrocortisone and prednisolone are highly useful in alleviating inflammation in individual

joints. The procedure represents local therapy which may serve as a valuable adjunct to, but not as a substitute for, systemic treatment It may be applied most advantageously under the following circumstances: (1) when the articular manifestations are restricted to one or a few joints; (2) when one or two joints in a multiple arthritis are particularly resistant to systemic therapy, (3) when, during the course of otherwise successful therapy, an acute flare-up of arthritis develops in one or two joints; (4) when only a few joints are incapacitating and complications such as pregnancy, diabetes, pulmonary tuberculosis, active peptic ulcer, etc. prohibit systemic therapy, and (5) as an auxiliary measure in the orthopedic correction of joint deformities, especially flexion contractures being treated by non-surgical methods

The adaptability of intra-articular therapy is restricted because the effects are local and usually temporary Symptomatic relief in the joint is usually prompt in its appearance (within 24 to 72 hours) but the completeness and duration of the effects vary considerably Immediate improvement may be anticipated in from 80 to 90 per cent of rheumatoid joints treated, and benefits may continue anywhere from a few days to several weeks, occasionally longer. At times a series of injections in a persistently troublesome joint (given at intervals of one to four weeks) provides more lasting benefits

Hydrocortisone acetate has been used more extensively than other available preparations Usually recommended doses range from 10 to 50 mg, the amount being determined by the size of the joint treated and the severity of inflammation present. From the author's recent experience, greater unit doses (i e, 100 to 200 mg for a large joint, such as a knee) may provide more complete and more lasting relief and often may be successful when smaller amounts yield an indifferent response Large milligram doses are technically feasible, even for small joints, with the more concentrated suspensions (50 to 200 mg. per cc) which are now manufactured The local effectiveness of many higher esters of hydrocortisone has been compared It has been reported that the longest average duration of action is promoted by the tertiary-butyl-acetate ester The local activity of prednisolone esters (acetate and tertiary-butyl-acetate) per milligram has been determined to be about twice as great as for similar esters of hydrocortisone In practical application, however, prednisolone preparations provide no advantages when equivalently effective dosages are employed

The intra-articular administration of steroid compounds is not without hazard To prevent joint injury and infection, the physician must be familiar with recommended techniques based on anatomical considerations and aseptic surgical precautions.

Selected Bibliography

Boland, E. W.. Clinical use of cortisone, hydrocortisone, and corticotropin. J A. M A *150*. 1281, 1952

—— Experiences with 9 alpha-fluorohydrocortisone acetate in rheumatoid arthritis. Ann New York Acad Sc *61*: 591, 1955

——: Prolonged uninterrupted cortisone therapy in rheumatoid arthritis Brit M J *2* 191, 1951

—— Antirheumatic effects of hydrocortisone (free alcohol), hydrocortisone acetate, and cortisone (free alcohol) as compared with cortisone acetate results from oral administration in patients with rheumatoid arthritis Brit M J *1* 559, 1952

——· Oral hydrocortisone in the treatment of rheumatoid arthritis M. Clin North America *38* 337, 1954

——. Present status of hydrocortisone as a therapeutic agent in rheumatoid arthritis. Ann New York Acad Sc. *61* 349, 1955.

—— Prednisone and prednisolone therapy in rheumatoid arthritis J A M A *160* 613, 1956

—— and Headley, N E Oral use of cortisone acetate J A. M A *115*· 8, 1951.

—— and ——: Management of rheumatoid arthritis with smaller (maintenance) doses of cortisone acetate J A M. A *144*: 365, 1950.

Bollet, A. J. Black, R L and Bunim, J. J Major undesirable side-effects resulting from prednisolone and prednisone J A M A. *158*. 459, 1955

Borman, A and Singer, F M Adrenocortical activity of 9-alpha halo derivatives of cortisone and hydrocortisone Federation Proc. *13*. 185, 1954

Bunim, J J, Black, R L., Bollet, A J and Pechet, M M: Metabolic effects of metacortandralone and metacortandracin Ann New York Acad Sc *61* 358, 1955

——, Pechet, M M and Bollet, A. J Studies on metacortandralone and metacortandracin in rheumatoid arthritis· antirheumatic potency, metabolic effects, and hormonal properties J A M A *157*. 311, 1955

——, Ziff, M and McEwen, C Evaluation of prolonged cortisone therapy in rheumatoid arthritis Am J Med *18* 27, 1955

Conn, J W., Lawrence, H L and Fajans, S S: The probability that Compound F (17-hydroxycorticosterone) is the hormone produced by the normal adrenal cortex Science *113*: 713, 1951

Demartini, F, Grokoest, A W and Ragan, C Pathological fractures in patients with rheumatoid arthritis treated with cortisone J A M A *149*: 750, 1952

DiRaimondo, V. C. and Forsham, P H. Some clinical implications of the spontaneous [illegible] Am J Med *21*, 321, 1956

[illegible] mat. Dis *2*: 5, 1951

[illegible] apy M Clin North America *35* 1229, 1951.

Fried, J. Biological effects of 9-alpha fluorohydrocortisone and related halogenated steroids in animals Ann New York Acad. Sc *61*: 573, 1955

—— and Sabo, E F.: 9 alpha fluoro derivatives of cortisone and hydrocortisone J. Am Chem Soc *76*· 1455, 1954

Freyberg, R H, Traeger, C. H, Adams, C H., Kuscu, T., Wainerdi, H and Bonomo, I: Effectiveness of cortisone administered orally. Science *112*: 429, 1950

——, ——, Patterson, M, Squires, W, Adams, C. H and Stevenson, C: Problems of prolonged cortisone treatment for rheumatoid arthritis further investigations. J A M A *147* 1538, 1951.

Hench, P S The reversibility of certain rheumatic and nonrheumatic conditions by use of cortisone or of the pituitary adrenocorticotropic hormone (Nobel Lecture) Ann Int Med *36* 1, 1952

——, Kendall, E. C., Slocumb, C. H and Polley, H F Effects of cortisone acetate and pituitary ACTH on rheumatoid arthritis, rheumatic fever and certain other conditions a study in clinical physiology Arch Int Med *85* 545, 1950

—— and Ward, L. E. Rheumatoid arthritis and other rheumatic or articular diseases *In* Medical Uses of Cortisone, ed by Lukens, F D W. New York, Blakiston, 1954

Hollander, J L. Local therapy of arthritis and related conditions intra articular hydrocortisone Merck Rep *62* 8, 1953

——, Brown, E M, Jr, Jessar, R A and Brown C Y Hydrocortisone and cortisone injected into arthritic joints comparative effects of and use of hydrocortisone as a local antiarthritic agent J A M A *147* 1629, 1951

——, ——, ——, Udell, L., Smukler, N M and Bowie, M A Hydrocortisone tertiary butyl acetate by intra articular injection J A M A *158* 476, 1955

Holley, H L. Adrenal cortical function and the pathogenesis of rheumatoid arthritis Ann Int Med *45* 550 1956

Ingle, D J and Kuizenga M H The relative potency of some adrenal cortical steroids in the muscle-work test Endocrinology *36* 218, 1945

Jacobsen, R P and Pincus, G The chemistry of adrenal steroids Am J Med *10* 531, 1951

Kendall, E C The adrenal cortex and rheumatoid arthritis Brit M J *2* 1295, 1951

Pabst, M L, Sheppard R and Kuizenga, M H Comparison of liver glycogen deposition and work performance tests for bio-assay of adrenal cortex hormones Endocrinology *41* 55, 1947

Polley, H F and Mason, H L Rheumatoid arthritis effects of certain steroids other than cortisone and of some adrenal cortex extracts J A M A *143* 1474 1950

Ragan, C. The undesirable side effects withdrawal symptoms and contraindications of the use of cortisone and ACTH in rheumatic diseases Bull Rheumat Dis *1* 5, 1950

Salassa, R M, Bennett, W A, Keating, F R, Jr and Sprague, R G Postoperative adrenal cortical insufficiency occurrence in patients previously treated with cortisone J A M A *152* 1509, 1953

Sokoloff, L., Sharp, J T and Kaufman, E H The adrenal cortex in rheumatic disease pathologic study with special reference to effects of cortisone and corticotropin Arch Int Med *88* 627, 1951

Sprague, R G, Power, M H Mason, H L., Albert, A, Mathieson, D R, Hench, P S, Kendall, E C, Slocumb, C H and Polley, H F Observations on the physiologic effects of 17 hydroxy 11 dehydrocorticosterone (cortisone) and of adrenocorticotropic hormone (ACTH) in man Arch Int Med *85* 199, 1950

Thorn, G W, Forsham P H, Frawley, T F, Hill, S R, Jr, Roche, M, Staehelin D, and Wilson, D L. The clinical usefulness of ACTH and cortisone New England J Med *242* 783, 824, 865, 1950

——, Jenkins, D, Laidlaw, J C, Goetz, F C., Dingman, J F, Arons, W L., Streeten, D H P and McCracken, B H Pharmacologic aspects of adrenocortical steroids and ACTH in man New England J Med *248* 232, 284, 323, 369, 414, 588, 632, 1953

Ziff, M., Scull, E., Ford, D McEwen, C and Bunim, J J Effects in rheumatoid arthritis of hydrocortisone and cortisone injected intraarticularly Arch Int Med *90* 774, 1952.

Aortic Insufficiency Associated with Rheumatoid Spondylitis

by Elam C. Toone, Jr., E. L. Pierce and Gordon Hennigar

FOR OVER 20 YEARS sporadic reports by a number of observers have appeared in the literature noting cardiac disease associated with rheumatoid spondylitis.[1-9] The most consistent lesion and the one which has attracted most attention has been that of lone aortic insufficiency.[1-6] Other manifestations noted have been cardiac enlargement, conduction defects, pericarditis, myocarditis and other valvular lesions. In a recent study Schilder, Harvey and Hufnagel,[6] while evaluating cases of aortic insufficiency for possible surgical correction, found an incidence of five cases of rheumatoid spondylitis in the first 100 cases of aortic insufficiency examined. In this report the interesting observation was made that not a single case of rheumatoid spondylitis associated with mitral stenosis was observed in several hundred patients examined over the past several years. Bauer[2] had previously stated: "To date, we have not seen this type of valvular heart disease (lone aortic regurgitation) in patients with only peripheral joint involvement." Increasing experience has shown that the primary site of damage is probably the root of the aorta, with dilatation of the aortic ring being a secondary development, and that the gross and microscopic appearance is very similar to that of syphilitic aortitis.[6, 12-15]

The purpose of this report is to present observations on seven cases of aortic insufficiency associated with rheumatoid spondylitis, all of whom were male, six white and one Negro. The material has been obtained from the McGuire Veterans Hospital—238 cases of rheumatoid spondylitis studied over a period of ten years, and the Medical College of Virginia—26 cases in five years.

The diagnosis of rheumatoid spondylitis has been made in each case on the basis of characteristic roentgen changes in the sacroiliac joints and lumbar spine, and typical symptoms and signs of the disease: back pain and stiffness, limited range of motion, spasm of the paravertebral muscles and often an associated reduced chest expansion. The diagnosis of aortic insufficiency has been made on the basis of a characteristic diastolic murmur heard over the aortic valve area and along the left sternal border by at least two observers (table 1).

TABLE 1

Case	Age	Peripheral Rheumatoid Arthritis	Acute Rheumatic Fever	Erythrocyte Sedimentation Rate	Serologic Test for Syphilis	Blood Pressure mm	Left Ventricular Hypertrophy by Roentgenogram	Electrocardiogram
1	54	yes	no	51	neg	140/50	yes	AV block, 1st degree LBBB LV strain
2	51	no	no	*	neg	160/80	yes	LV strain
3	51	yes	no	21	neg	175/75	yes	AV block, 1st degree, Wenckebach
4	48	yes	no	30	neg	120/50	yes	AV block, 1st degree
5	62	no	possible	10	neg	160/75	yes	LV strain
6	32	no	no	26	neg	182/80	no	normal
.	52	yes	no	30	neg	140/10	yes	LBBB LV strain

*CR protein 1, angina 1 and 7, pericarditis 1, iritis 3 and 1?

Case No. 1—R E.H., a 54 year-old colored male, was admitted to St. Philip Hospital in July, 1956, complaining of exertional dyspnea and orthopnea of two weeks' duration, associated with pain and stiffness in the lower back, the knees, shoulders, wrists and hands. Treatment consisted of the use of digitalis, mercurial diuretics and x ray therapy to the lumbosacral spine with satisfactory improvement and discharge after two weeks' hospitalization. The patient was readmitted in September, 1956 in acute pulmonary edema which resulted from the voluntary discontinuance of digitalis. Response to treatment with digitalis and mercurial diuretics was again prompt and satisfactory, and the patient was discharged after one week. The final admission occurred in December, 1956 because of severe substernal pain. Vigorous treatment for the acute congestive failure was instituted and nitroglycerin was given, without benefit, for the substernal pain. The patient's condition grew progressively worse with Cheyne-Stokes' respiration developing, and death occurred five days after admission.

The past history revealed the following: Hospitalization in February, 1953, because of fever, chills, productive cough, weight loss and generalized stiffness and aching in the muscles and joints of eight weeks' duration. The following diagnoses were made. (1) pericarditis—based on the presence of a friction rub and electrocardiographic changes, (2) first degree heart block; (3) rheumatoid arthritis, possible—based on x-ray changes, (4) abdominal pain of an unexplained nature and leading to an exploratory laparotomy with negative findings. Hospitalization in July, 1953, because of malaise, anorexia, anterior chest pain, fever, and shortness of breath on exertion. The diagnoses: (1) pneumonitis, left lower lobe; (2) urethritis; (3) conjunctivitis (iritis), and (4) recurrent pericarditis. Hospitalization in November, 1954, because of a productive cough, dyspnea on exertion and intermittent swelling of his knees and ankles. The diagnoses included (1) conjunctivitis, (2) stomatitis, (3) recurrent arthritis, type undetermined, and (4) fever, undetermined origin.

A past history of rheumatic fever or syphilis was denied.

Physical examination (July, 1956). The blood pressure was 140/50, the pulse rate 100, rhythm regular, and temperature 102°F. The cardiac apex was in the sixth intercostal space in the anterior axillary line. There was a Grade 3, high pitched, decrescendo diastolic murmur heard loudest at the third left intercostal space but present also over the aortic valve area and along the entire left sternal border. A Grade 2, soft, blowing systolic murmur was heard at the apex. Rales were present in both lung bases. The liver was moderately enlarged and tender. The back was limited in its range of motion in all directions, and forward flexion was to within 10 inches of the floor. There was a moderate atrophy with spasm of the paravertebral muscles. Chest expansion was ¾ths of an inch. The wrists were enlarged and limited in their range of motion, both for flexion and extension. Both shoulders were limited for abduction and external rotation, and there was moderate synovial thickening of both knees. Small, firm, freely movable nodules were present over both elbows.

The x ray showed a grossly enlarged heart with a hypertensive configuration and a moderately arteriosclerotic aorta (fig. 1). There was moderate pulmonary congestion and a small amount of fluid was present in the right pleural cavity. An electrocardiogram showed evidence of left ventricular strain and a left bundle-branch block. X rays showed the sacroiliac joints to be irregular and narrowed with areas of bone production and bone destruction (fig. 2). On the anterior margin of the third lumbar vertebra, a small area of calcification was noted, suggesting early calcification of the anterior ligament. These changes were interpreted as those of early rheumatoid spondylitis. The x ray of the right wrist and hand showed the changes of a moderately advanced chronic

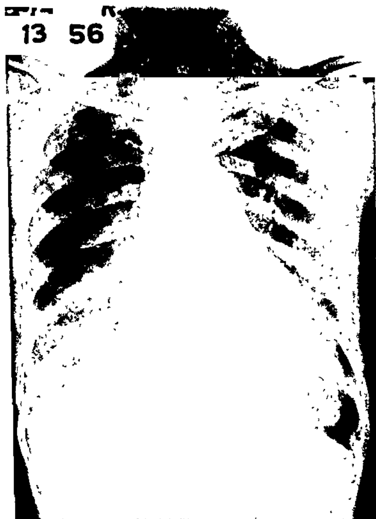


Fig 1 Roentgenogram of the chest of case 1 There is general cardiac and left ventricular enlargement, moderate pulmonary congestion and a small amount of fluid in the right pleural cavity

arthritis (rheumatoid) The serologic test for syphilis was negative; the erythrocyte sedimentation rate (ESR) was 51 mm; sheep cell agglutination was negative, the antistreptolysin titre was less than 50, the lupus erythematosus (LE) cell preparation

was negative, the C-reactive protein was 2+; total protein was 7.4 Gm, the albumin was 2.8 Gm, the globulin was 4.6 Gm, the hemoglobin was 13.5 Gm, and the white blood cell count was 6,800



FIG 2. Roentgenogram of the pelvis of case 1. The sacroiliac joints are irregular and narrowed and show areas of bone production and bone destruction

Clinical diagnoses included: (1) rheumatoid spondylitis; (2) aortic insufficiency, (3) congestive heart failure; (4) peripheral rheumatoid arthritis, possible; (5) coronary artery disease with coronary insufficiency, possible; (6) mitral insufficiency, possible

Pathology report

Gross inspection showed an immensely dilated and hypertrophied left ventricle,

globoid in shape, the trabeculae carneae flattened, and the appearance typical of aortic regurgitation (fig 3) The aortic ring measured 10 mm, the commissures were widened, the free margins of the aortic valve were opaque, slightly cartilaginous, free of calcification and atheroma, and were rolled and contained a few small nodules The right coron



Fig 3 Dilated and hypertrophied heart with flattened trabeculae carneae. The appearance of the myocardium with dilated aortic valve is pathognomonic of aortic regurgitation

Fig 4 Thickened, slightly nodular aortic cusps wi[illegible] [illegible]es The right coronary artery orifice is pulled above the sinus of Valsalva by [illegible] and medial fibrosis

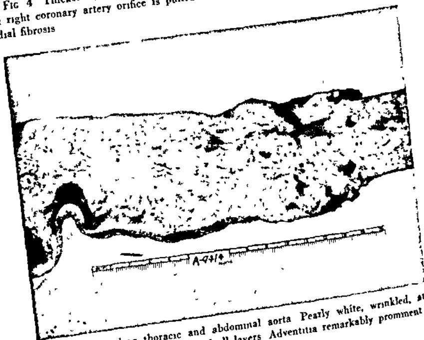


Fig 5 Descending thoracic and abdominal aorta Pearly white, wrinkled, atheromatous free intima and thickening of all layers Adventitia remarkably prominent and edematous

ary artery orifice was slightly narrowed by intimal changes, and had been pulled upward by the scarring process (fig. 4). The aorta from the superior margin of the sinuses of Valsalva to the renal arteries of the aorta was dilated, and the wall greatly thickened The first portion of the aorta was obviously more involved than the remainder (fig 5).

Microscopically the intima was thickened, scarred, pearly gray, showed a prominent subendothelial zone of fibrin, and contained inflammatory foci and microabscesses (figs. 6 and 7). The media contained areas of acute chronic inflammation with microabscesses. Polymorphonuclear leukocytes were present around the zones of necrosis, while lymphocytes and plasma cells infiltrated in other areas, particularly the perivascular areas. Moderate metachromasia of the media was demonstrated with toluidene blue stain, and small areas of destruction of the elastic tissue, replaced by linear scars, with Verhoeff van Gieson stain (figs 6, 8, and 9) The adventitia was edematous and approximately four times normal thickness and showed changes of endarteritis obliterans of the vaso vasorum associated with areas of perivascular lymphocytic infiltration and extensive fibrosis (figs 6 and 10). There was an extensive chronic fibrous pericarditis with foci of "fibrinoid degeneration," and areas of acute inflammation with small areas of perivascular fibrosis in the myocardium The endocardium was not affected

Sections of representative joints throughout the entire body were examined Evidence of scarring and increased vascularization was present with a few inflammatory cells seen in and around small arterioles and capillaries The most profound scarring was found in the sacroiliac joints There was destruction of the articular cartilage and fibrous union of the bones (fig 11)

The subcutaneous nodule showed fibrinoid changes, and it was felt that this might

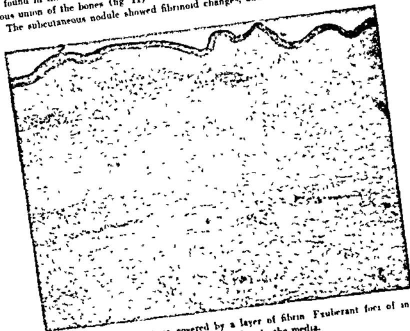


Fig. 6. Aorta with intima covered by a layer of fibrin Exuberant foci of inflammation are present in the intima and smaller foci in the media.



FIG 7 Microabscesses in the intima Such microabscesses are seldom if ever seen in syphilitic aortitis

represent a healing rheumatoid nodule, although the typical features of palisading were absent (fig 12).

Anatomical diagnoses (1) Rheumatoid (ankylosing) spondylitis; (2) Rheumatoid aortitis leading to aortic regurgitation, (3) Healing subcutaneous nodule, possibly of a rheumatoid nature

Case No 2—T K J, a 51-year-old white male, was admitted to the Medical College of Virginia Hospital in September 1956 because of pain and coldness in the fingers, stiffness of the back, difficulty in standing and walking, and shortness of breath when emotionally upset The pain in the fingers was described as a constant, aching discomfort made worse when the fingers were chilled There was no description of change in color, no limitation of motion, and no swelling, redness or increased heat in any of the joint areas The back stiffness, pain, difficulty in standing and inability to walk had been noted over a period of some two years For 10 years the blood pressure had been known to be elevated and eight years prior to this admission the patient had suffered a cerebrovascular accident which had left him aphasic

A past history which suggested syphilis, rheumatic fever, iritis or pericarditis was denied

Physical examination. The blood pressure was 160/80; pulse rate 60 per minute, rhythm regular, and temperature 98 4° F The cardiac apex was located in the sixth intercostal space in the mid-clavicular line There was a Grade 4 aortic decrescendo diastolic murmur heard best along the left sternal border in the second, third and fourth interspaces A Grade 2 mitral systolic murmur was heard at the apex. The chest



FIG. 8 Focal linear loss of elastic tissue with replacement fibrosis in the media Verhoeff van Gieson stain

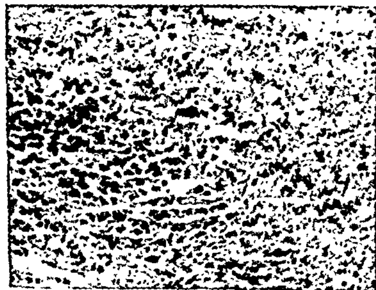


FIG. 9 Similar lesion to figure 5, but located in the media.

expansion was limited but could not be measured The spine was fixed and the range of motion markedly reduced in all directions There was no swelling, redness, tenderness, or limitation of motion in any of the peripheral joints

The x-ray examination showed the heart to be enlarged with a *slightly hypertensive* configuration and left ventricular hypertrophy (fig 13). The electrocardiogram was interpreted as showing left ventricular hypertrophy X rays of the lumbar spine showed advanced changes of rheumatoid spondylitis and calcification of the anterior and longitudinal ligaments of the lumbar spine (fig. 14). The serologic test for syphilis was negative, the C-reactive protein 1+; and the hemoglobin was 9.4 Gm.

Diagnoses included (1) rheumatoid spondylitis; (2) aortic insufficiency; (3) possible mitral insufficiency, (4) possible Raynaud's disease

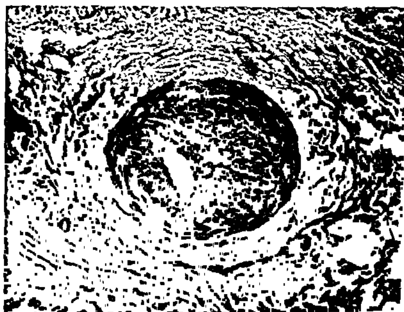


Fig 10 Vaso vasorum showing intimal fibrosis or endarteritis obliterans and chronic perivascular inflammation rich in lymphocytes and some plasma cells. This lesion is seen in both syphilitic and rheumatoid aortitis

Case No 3—W R F., a 51 year-old white male, was admitted to the McGuire Veterans Hospital in August, 1956 for re evaluation and treatment of his arthritis. There was a history of joint disease having begun in 1934 and of multiple admissions to the McGuire Veterans Hospital since 1948 A diagnosis of peripheral rheumatoid arthritis and rheumatoid spondylitis had been made Six weeks prior to the present admission, the left eye had become acutely inflamed and the diagnosis of iritis was made This was followed by an exacerbation of pain, swelling and stiffness in the wrists and ankles The symptoms were more marked in the peripheral joints than in the spine During this interval there had also been symptoms which the patient attributed to his heart; weakness, dizziness, palpitation and moderate shortness of breath on exertion

A past history of syphilis, rheumatic fever, angina or pericarditis was denied

Physical examination: The blood pressure was 175/75, the pulse rate 84, the rhythm regular and the temperature 98.6° F The cardiac apex was in the fifth intercostal space 12 cm from the mid sternal line There was a Grade 1 decrescendo diastolic murmur heard over the aortic valve and along the left and right sternal borders. The chest expansion was 1¼ inches and forward flexion was to within 5 inches of the floor The gait was slow and halting due to pain in the feet, ankles and knees and to the stiffness in the back The lumbar curve of the spine was straightened, and the hands were held in flexion with evidence of early ulnar deviation The right shoulder was approximately 1 inch higher than the left.

X ray examination showed a moderate left ventricular hypertrophy The electrocardiogram showed evidence of a first degree heart block and a Wenckebach phenomenon X rays of the sacroiliac joints showed almost complete obliteration with increased bone production in this area There was calcification of the lateral and anterior ligaments of



Fig. 11 Sacroiliac joint showing bone destruction and replacement of the cartilage by fibrous tissue

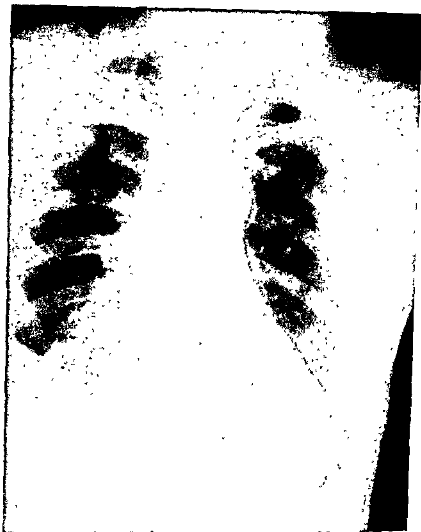


FIG 13 Roentgenogram of the chest of case 2 There is general cardiac and left ventricular enlargement

sacroiliac joints with areas of bone production and bone destruction resembling small cystic areas The paravertebral ligaments in the lumbosacral area were calcified The serologic test for syphilis (STS) was negative, the erythrocyte sedimentation rate (ESR) was 26 mm, and the hemoglobin was 14.2 Gm

Diagnoses included: (1) rheumatoid spondylitis, (2) aortic insufficiency

Case No 7—T W K, a 52 year old white male, was admitted to McGuire Veterans Hospital in September, 1952 because of severe pain in the lower back and both shoulders for approximately two years A number of physicians had been consulted during this



Fig 14 Roentgenogram of the pelvis of case 2 Almost complete obliteration of the sacroiliac joints and calcification of the lateral ligaments of the lumbar vertebrae are apparent

time, and extensive x ray examinations had been made Diagnoses offered had been varied but not consistent, and in part, included such as "neuritis," "sacro iliac spasm," and "arthritis of the back" In 1950, during the course of an insurance examination a heart murmur was detected and the patient was told that it was due to a "leakin valve" The following year he developed a sudden onset of chest pain, extreme dyspne

associated with vertigo and was hospitalized for a period of 10 weeks During this time he was treated with oxygen and was given nitroglycerin and digitalis He was told at this time that he had "a heart block" Hospitalizations occurred on two additional occasions, each because of severe dyspnea and weakness Maintenance treatment consisted of the use of digitalis and mercurial diuretics Approximately 12 years prior to this hospitalization, the left knee suddenly became painful and swollen This condition lasted approximately two months There was no history of trauma or any other associated illness The condition subsided and has not recurred



FIG 15 Roentgenogram of the chest of case 5 There is enlargement of the left ventricle and widening of the aortic shadow

A past history of syphilis, rheumatic fever, pericarditis or iritis was denied.

Physical examination. The blood pressure was 140/100, the pulse rate was 80, the rhythm regular, and temperature 98.6°F. The cardiac apex was in the sixth intercostal space, 10 cm. from the mid-sternal line. A Grade 3 aortic systolic and a Grade 3 blowing decrescendo diastolic murmurs were heard over the entire precordium, but were accentuated in the third left intercostal space adjacent to the sternum. A high pitched systolic murmur was heard at the apex. Corrigan pulse and Duroziez' sign were present.



Fig. 16. Roentgenogram of the pelvis of case 5. Obliteration of the sacroiliac joints and calcification of the lateral ligaments of the lumbar spine are apparent.

The back was almost completely fixed and rigid with only a slight degree of forward flexion possible The left shoulder was restricted in its range of motion for abduction and rotation

The x-ray examination showed a heart with an enlarged transverse diameter and elongation of the left ventricular segment The electrocardiogram revealed a left bundle-branch block and evidence of left ventricular strain The sacroiliac joints were described *as appearing hazy and fused* There was marked osteoporosis of the lumbar vertebrae and bones of the pelvis Osteoporosis was marked in the bones which made up the left shoulder joint and in the hands and wrists The serologic test for syphilis (STS) was negative, the erythrocyte sedimentation rate (ESR) was 30 mm ; and the hemoglobin was 12 1 Gm

Diagnoses included (1) rheumatoid spondylitis; (2) aortic insufficiency; (3) mitral insufficiency, and (4) peripheral rheumatoid arthritis

Since the most common age at which rheumatoid spondylitis develops is between 20 and 25 years, the ages represented in this group would suggest that aortic insufficiency does not usually develop until the disease has been present for several years. Even in case 6, in which the aortic regurgitation was first found at the age of 32, the history indicated that the spondylitis began some eight years previously. A possible exception to this is case 1, in which a history of joint disease extended over a period of only three years, and the x-ray changes in his sacroiliac joints and lumbar spine indicated a relatively recent development of the spondylitis. Our records were not sufficiently detailed to give us exact information as to the onset of the rheumatoid spondylitis, and we have omitted this from our data.

Peripheral rheumatoid arthritis was present in four cases, which is a somewhat higher proportion than reported by Schilder et al,[8] and less than that reported by Bauer and Clark.[2] The limited number of cases observed in this series would make this of no statistical value, however. The erythrocyte sedimentation rate (Cutler) was elevated in five of the seven cases, normal in one, and not recorded in the seventh; in this case the C-reactive protein was 1+ Iritis had been and was present in one case (case 3), and questionably in another (case 1). In this instance repeated references were made to the presence of a conjunctivitis, but nowhere in the record was the term iritis applied to the lesion. Small subcutaneous nodules were noted in the region of both elbows in one patient (case 1) and clinically appeared to be typical of the subcutaneous rheumatoid nodule. Histologic examination, however, did not fully substantiate this clinical impression

"The nodule consisted of fibroblastic proliferation, histiocytes, lymphocytes and plasma cells. There was a vague organoid appearance suggesting the features of an old rheumatoid nodule. However, palisading was not a prominent feature, being seen here and there. In the center of the nodule was amorphous hyalin-fibrinoid "

In all instances, there was a negative history of syphilis or of treatment

for this condition. The serologic test for syphilis (STS) reaction was negative in every case. A positive history of rheumatic fever was not obtained in a single instance. In case 5, rheumatic fever was a possible diagnosis The joint disease began in 1918 with a migratory polyarthritis but established itself shortly as a chronic back disability. Shortly after this episode a diagnosis of "an enlarged heart" was made. There had been no previous diagnosis of valvular heart disease In three patients (cases 1, 2 and 7), an apical systolic murmur that might be interpreted as mitral insufficiency was present In one of these (case 1), a postmortem examination was performed No evidence of mitral valvular disease was noted (table 1)

The pulse pressure was in excess of 50 mm of mercury in each case In two (cases 6 and 7) there were peripheral signs of aortic insufficiency (capillary pulsations in the nail beds and Duroziez' sign). X-ray examination of the heart showed evidence of left ventricular hypertrophy in each case except one (case 6) One patient (case 1) had evidence of congestive heart failure six months prior to death. Death occurred as a result of this condition. A second patient (case 7) had been treated on several occasions for congestive failure over a period of two years. One patient (case 3) was apprehensive about his heart because of symptoms consisting of palpitation, an irregular pulse, spells of dizziness, and moderate shortness of breath Chest pain of an anginal type was noted in two cases (cases 1 and 7) Each had been treated with nitroglycerin, one with relief and one with no relief Pericarditis was noted clinically in one case (case 1) and was confirmed on pathologic examination Four cases presented electrocardiographic evidence of conduction defects either in the form of a first degree A-V block (cases 1, 3 and 4), or a left bundle-branch block (cases 1 and 6) There was a Wenckebach's phenomenon in one case (case 3) Four cases (cases 1, 2, 5 and 7) showed, in addition, an electrocardiographic pattern of left ventricular strain In only one (case 6) was the electrocardiographic pattern considered to be within normal limits.

COMMENT

As experience becomes greater, the clinical pattern established in cases of aortic insufficiency associated with rheumatoid spondylitis is becoming more definite Usually, the rheumatoid spondylitis will have been present for several years and often there is a history of recent treatment for an exacerbation of the condition Peripheral rheumatoid arthritis is often encountered and iritis occasionally The cardiovascular findings, in addition to the diastolic murmur of aortic insufficiency, consist of the following. a wide pulse pressure, evidence of left ventricular hypertrophy, and very often electrocardiographic evidence of conduction defects—usually an A-V or left bundle-branch block. Anginal-like pains and pericarditis may be encountered.

Initially, it was felt that aortic insufficiency represented a relatively benign valvular lesion.[3, 4] Subsequent experience has proven this not to be so[5, 6] Congestive heart failure seems to be a relatively common and early development and the prognosis seems to be poor. Rheumatic fever, either past or present, appears to have been present in only a few instances and syphilis has never been established as a serious possibility on the basis of negative histories and consistently negative serologic test for syphilis (STS) reactions

There is also evolving a pathologic pattern which is fairly predictable and consists of the following. (1) a dilated incompetent aortic ring; (2) thickened aortic valve cusps with minimal fusing and rolling; (3) inflammatory aortitis with dilatation and histologic changes more characteristic of luetic than rheumatic aortitis, and (4) patent coronary orifices. The pathologic findings in the case reported (case 1) are unusual in that the process is not limited to the ascending aorta, but involves the area from the sinuses of Valsalva to the renal arteries. Clark, Kulka and Bauer[14] state: "The lesion ('rheumatoid aortitis') mimics that of syphilitic heart disease, but tends to remain localized to the region of the aortic valve and rarely, if ever, involves the aorta distal to the ascending portion" We are of the opinion that the type of focal inflammatory changes seen in the intima and media which have been designated as microabscesses (figs. 7 and 8) is the morphologic pathognomonic feature of this disease It does not in any way resemble a gumma. The remaining histologic features are shared by syphilitic aortitis, and this is particularly true of the mucinous fibrotic thickening of the adventitia.

The gross appearance did not suggest syphilitic aortitis because of the lack of calcific atheromatosis, and the absence of marked transverse and longitudinal wrinkling. Furthermore, since the rolling of the free edge of the aortic cusps has been seen in old healed rheumatic valvulitis, it was not considered grossly pathognomonic of syphilis The customary shortening of the aortic flaps in syphilitic valvulitis with regurgitation was absent. In summary, it may be stated that, whereas the appearance of the adventitia is strongly suggestive of a syphilitic aortitis, the changes in the intima are not those of a luetic lesion This produces what might be termed an intimal-adventitial dissociation.

SUMMARY

Aortic insufficiency was observed in seven cases during the course of examinations made on 264 cases of rheumatoid spondylitis. There was no evidence of syphilis in any of the seven cases, a questionable history of rheumatic fever in one, and evidence of peripheral rheumatoid arthritis in four

Rheumatoid spondylitis was diagnosed by typical roentgenographic

changes in the sacroiliac joints and aortic insufficiency by the diastolic murmur heard over the aortic valve area and along the left sternal border by at least two observers.

In addition to the diastolic murmur of aortic insufficiency and the wide pulse pressure, the following cardiac manifestations were noted: left ventricular enlargement and strain, first degree heart block, left bundle-branch block, Wenckebach's phenomenon, pericarditis, angina pectoris-like pain and congestive heart failure.

Pathologic examination of one case showed not only involvement of the root of the aorta but extensive damage to the level of the renal arteries. The changes were of an inflammatory character and resembled the lesions seen in syphilis rather than those associated with rheumatic fever or rheumatoid arthritis

The findings in these cases and a review of those previously reported indicate a specific relationship between the rheumatoid spondylitis and the aortitis The aortitis and aortic insufficiency are often associated with damage to the myocardium and pericardium but with no other valvular lesion. A serious burden is placed on cardiac function and the prognosis is poor This type of change has not been reported in cases of peripheral rheumatoid arthritis unless associated with rheumatoid spondylitis

References

1. Bauer, W., Clark, W. S., and Kulka, J. P. Aortitis and aortic endocarditis, unrecognized manifestations of rheumatoid arthritis. Ann. Rheumat. Dis. 10: 470, 1951
2. Clark, W. S. and Bauer, W. Cardiac changes in rheumatoid arthritis. Ann. Rheumat. Dis. 7: 39, 1948
3. Bernstein, L. Cardiac complications in spondylarthritis anklyopoetica. Rheumatism 7: 18, 1951
4. Bernstein, L. and Brock, O. J. Cardiac complications in spondylarthritis ankylopoietica, Acta med. Scandinav. *135*: 185, 1949
5. Blumberg, Baruch and Ragan, C. The natural history of rheumatoid spondylitis. Medicine 35: 1, 1956
6. Schilder, D. P., Harvey, W. P., and Hufnagel, C. A. Rheumatoid spondylitis and aortic insufficiency. New England J. Med. 255: 11, 1956
7. Glecker, W. J. Rheumatoid spondylitis with carditis. Am. J. Med. 16: 284, 1954
8. Herrick, W. W. and Tyson, T. L. The medical aspects of ankylosing spondylitis (Marie Strumpell). Ann. Int. Med. *15*: 994, 1941
9. Krebs, W. and Wurm, H. Die Bechterewsche Krankheit, ed. P. Jurgens. Dresden Steinkopff, 1938
10. Fraser, T. N. Ankylosing spondylitis in sisters. Ann. Rheumat. Dis. 9: 231, 1950.

11 Sokolow, M and Snell, A. M Atypical features of rheumatic fever in young adults. J.A.M.A 133 981, 1947
12 Case 323, Medical Grand Rounds Massachusetts General Hospital Aortitis and aortic valve disease in rheumatoid arthritis Am. Pract. & Digest Treat 6, 1236, 1955
13 Case Records of the Massachusetts General Hospital. New England J Med 214, 693, 1936
14 Clark, W S, Kulka, J. P., and Bauer, W.: Rheumatoid aortitis with aortic regurgitation Am J Med 22 580, 1957.
15 Valaitis, J, Pilz, C G, and Montgomery, M M: Aortitis and aortic valve insufficiency in rheumatoid arthritis Arch Path 63: 207, 1957

Phenylbutazone (Butazolidin) in the Treatment of Acute Arthritis

by R. H Freyberg

For many years efforts have been made either to develop drugs possessing greater analgesic effects than those currently available or to find means of using the available drugs more effectively Many derivatives of salicylic acid and of the coal-tar substances have been produced, while variants of the pyrazole group of drugs have also been prepared. One of the pyrazole derivatives is phenylbutazone, prepared commercially under the trade name Butazolidin. Stenzl[1] produced this substance first in 1948. It was employed as a solubolizing agent for amidopyrine and was mixed with this chemical in order that it might be injected parenterally for therapeutic purposes Later it was studied for its inherent therapeutic effects.

Chemistry. Phenylbutazone is 3, 5-dioxo-1, 2-diphenyl-4-n-butyl pyrazolidine and is similar, chemically, to aminopyrine, as illustrated in the structural formulae (fig. 1) It is a white crystalline powder and is insoluble in water, but it may be dissolved in alkalies, ethyl alcohol and other organic solvents.

Pharmacology. Phenylbutazone, like other pyrazole compounds, has several biologic effects. One of the most important is its analgesic action This is comparable to that of salicylates, other pyrazoles and phenacetin,

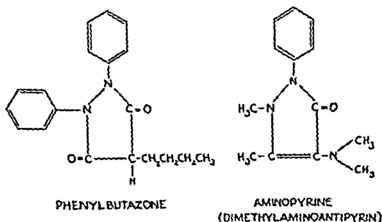


Fig. 1 Structural chemical formulae for phenylbutazone and amino pyrine

but inferior to that of morphine.[2] It is endowed with an antirheumatic action as well as an antihistaminic effect.[2, 3] In experimental animals, the anti-inflammatory action of phenylbutazone has been demonstrated by delay or inhibition of erythema that would have followed exposure to ultraviolet light and by inhibition of edema which normally follows injection of formalin or egg albumen into the rat's paw.[2] Phenylbutazone causes significant sodium retention, which results in a decrease in the urine volume and frequently in edema. The sodium retention is believed to be related to depression of renal tubular function.[4] Another result of tubular depression is a substantial increase in uric acid secretion and a considerable reduction in plasma urate.[5-8]

CLINICAL EXPERIENCE IN ACUTE RHEUMATIC DISORDERS

Phenylbutazone has proved to be beneficial in providing relief from several types of acute rheumatic maladies

Gouty Arthritis

A number of investigators have reported excellent antirheumatic effects from phenylbutazone administered early in an attack of gouty arthritis[7-15] The experience of selected American physicians is shown in table 1. Inspection

Table I

Summary of Results of Phenylbutazone Treatment of Acute Gouty Arthritis by Different American Investigators

Investigator	*Number of Patients*	*Number of Attacks*	*Dose*	Response: Relief in less than 7 days	Response: Relief after 7 days
Gutman & Yü[9]	16	20	400 to 800 mg daily, orally	13	7
Kidd, Boyce & Freyberg[9]	16	40	400 to 800 mg daily, orally or 400 to 1000 mg daily I M	30	10
Byron & Orenstein[11]	8	8	400 to 800 mg daily, orally	7	1
Kuzell et al[11]	200	200	200 to 1600 mg daily, orally or 1000 mg daily I M	168	32
Steinbrocker[12]	14	16	400 to 800 mg daily, orally or 600 to 1000 mg. daily I M	13	3
MacKnight[14]	11	11	200 to 600 mg daily, orally	10	1
Johnson et al[15]	10	20	200 to 600 mg daily, orally	16	4

of the tabulated results indicates the dependability of phenylbutazone The manner in which the action occurs indicates that it is too rapid to be the result of the excretion of urate in urine and lowering of the plasma urate content, even though this uricosuric action is a consistent and rather expeditious effect.

The action of phenylbutazone is not only analgesic; it is, in addition truly antirheumatic (anti-inflammatory). Soon after the administration of the drug is begun in patients with acute synovitis, pain usually diminishes and the signs of inflammation begin to subside Depending upon the schedule of administration the time required for complete suppression of the attack varies, but it is always relatively rapid and within a period of from 24 to 72 hours. If the synovitis has been present for several days before treatment, benefits occur more slowly Sometimes from 7 to 14 days of treatment may be needed before the inflammation becomes suppressed completely.

The method of administration varies with different clinicians, there is close similarity in dosage, however Based upon individual experience, this author has arrived independently at a schedule of dosage similar to that reported to be most successful by Smyth.[7, 11] As soon as there is evidence that a gouty attack is underway, the patient is given 600 mg of phenylbutazone orally. This initial large dose has been shown by Smyth to result in a more rapid rise in the blood phenylbutazone level and more rapid relief of articular distress Two hours after the initial dose and again four hours after the first dose, an additional 200 mg of phenylbutazone is given Thus, within four hours on the first day of an attack, 1000 mg of phenylbutazone is given. Improvement usually is noted within a few hours after the initial dose of the drug. Beginning on the second day and continuing until all signs of inflammation have disappeared, 100 mg of phenylbutazone is given three or four times daily depending upon the severity of the attack According to this method of treatment, Smyth[7] observed that pain began to subside within a period of from two to four hours The pain was controlled in 56 of 58 attacks of gout within 24 hours. All evidence of disease subsided within 72 hours in 47 of 51 attacks. Seldom is medication required after the fourth day.

Phenylbutazone administered in this manner does not usually lead to any undesirable side effects However, nausea, epigastric irritation and anorexia are experienced by some patients Such difficulties should be obviated by the administration of the drug intramuscularly instead of orally An intragluteal injection of 600 to 1000 mg of the drug in a 20 percent aqueous solution daily or 300 to 500 mg twice daily until it is no longer needed, has been satisfactory in such instances There is no greater speed of suppression of the attack as a result of intramuscular injection; this route merely eliminates the indigestion

Differences of opinion exist among experienced clinicians as to whether phenylbutazone has superiority over colchicine in the treatment of an acute attack of gout. Both have approximately an equal, excellent effect in most patients. Hence, the choice is usually dependent upon the side effects of each drug Although most serious toxic effects of phenylbutazone are encountered during prolonged administration of phenylbutazone, sensitivity reactions are encountered occasionally when a small amount of the drug only is given during a two or three day period for acute articular gout. For this reason, if colchicine is tolerated well,[15] it is generally preferred since it is effective. Some physicians prefer phenylbutazone because of its speed in producing relief and because of the absence of severe indigestion and diarrhea so commonly encountered after therapeutic doses of colchicine are administered. Regardless of differences in personal preference for the initial drug of choice to be used to suppress a gouty attack, it is reassuring to know that no longer is colchicine the only drug available for treatment of acute gouty arthritis. Since phenylbutazone is a reliable suppressive agent, if colchicine is poorly tolerated or ineffective, the first mentioned drug can usually be used with excellent results Indeed, the simultaneous use of phenylbutazone and colchicine has been found to be the most effective medicinal treatment for selected severe attacks of gout [16]

Acute Rheumatic Fever

Approximately 25 years ago the use of aminopyrine in patients with acute rheumatic fever was reported to be effective both as an antipyretic and an analgesic agent. It is not surprising, realizing the similarity of the nature of the drugs, that phenylbutazone also should be found to be beneficial in the treatment of acute rheumatic fever. The author has had no experience with the use of phenylbutazone for this rheumatic disorder. Numerous reports, however, indicate that it is effective in doses of from 400 to 600 mg daily.[8-21] Joint pains and temperature are improved rapidly In some instances the sedimentation rate is reduced; in other instances it remains unchanged. Patients experience a good recovery. According to the study of Fleming and Will,[19] five patients responded well to phenylbutazone after salicylates had proved unsatisfactory From the reports, it is strongly suggested that the therapeutic effect of phenylbutazone is equal and in some cases superior to that of salicylates for rheumatic fever. During many weeks of administration of phenylbutazone, problems of toxicity might be more numerous and severe than would be encountered with salicylates Hence, salicylates probably will remain the drug of choice for the treatment of rheumatic fever. Should salicylates be ineffective, however, phenylbutazone may be a reasonable substitute

Traumatic Arthritis

This form of acute arthritis usually requires an effective analgesic, and regardless of the extent of the pathology, pain usually is a problem. When narcotics are not needed, one of the salicylic acid derivatives may be effective. Another choice would be phenylbutazone. In doses of 200 mg. three times daily for a few days and reduced as the pain lessens, the drug has been found to be a satisfactory analgesic.[20]

Palindromic Rheumatism

Frain and Morris[22] give a good record of phenylbutazone in the treatment of palindromic rheumatism. Although *helpful as an analgesic during an attack*, there is no evidence that it alters the course of the disease or lessens the frequency of attacks.

Acute Nonarticular Rheumatic Disorders

Closely akin to its use for different forms of acute arthritis phenylbutazone has been employed effectively to relieve several types of nonarticular rheumatism. For acute bursitis, tendonitis or periarthritis as manifested in the acute painful shoulder syndrome, most clinicians employed the drug much as it is used to suppress an acute attack of gout. Various results have been reported. A complete remission in 10, major improvement in 24, minor improvement in 7 and no change or worsening in 14 patients was noted by Kuzell and collaborator[22] in a study of 64 patients. Strazza and Ressetar,[18] in a study of 19 patients, noted that 13 experienced complete and prompt remission, 4 showed marked improvement while 2 received little or no benefit. Eleven of 12 patients reported by Smith and Kunz[23] experienced rapid and complete relief. McCormick[24] reported that each of 14 cases was relieved within 48 hours. Byron and Orenstein[19] studied 21 cases of nonarticular rheumatism. Complete relief was noted in 15, major improvement in 3 and little or no response in 3. Among 6 patients of Steinbrocker and associates,[25] 2 had complete relief from pain and recovery of function, 3 showed great improvement, 1 had only minor benefit. Four of the 5 patients treated by Kelly[26] experienced "dramatic" relief.

Phenylbutazone in doses of 200 mg. three times daily has lead to satisfactory relief of pain in other less well defined rheumatic conditions, such as acute low back strain or lumbar myofibrositis.[20, 22, 25] Rapid relief has been reported from phenylbutazone in instances of epicondylitis[21] and herniated disc with sciatica.[18, 2] It is of little[25] or no value[27] in the management of neuralgia.

Toxicity

The use of phenylbutazone is always attended by the risk of develop-

ment of one or more forms of drug toxicity or hypersensitivity, some of which may be serious. Deaths from phenylbutazone have been reported The toxic effects of phenylbutazone deserve careful scrutiny and discussion The incidence of toxic reactions has been computed almost invariably in the total experience of *each investigator; in most instances the drug* was used daily for many weeks or months Although the occurrence of severe toxicity is unusual when this drug is administered for a period of less than ten days, nausea and vomiting frequently occur. In one of the author's patients the result was an acute gastric ulcer perforated on the morning after the last dose (200 mg.) of phenylbutazone, which had *been given over a* two-day period. A grand total of only 800 mg of the drug had been administered. Agranulocytosis has been reported after 7 days only of phenylbutazone administration

Mauer[29] has reviewed extensively the literature on toxicity of phenylbutazone Of the total of nearly 4000 patients, 1199 exhibited 1543 different forms of toxicity. There were twenty-three deaths attributed to the drug The fatalities were reported to be due to granulopenia, peptic ulcer with perforation or bleeding, exfoliative or other generalized dermatitis, anuria from urate plugs in ureters, nephritis, aplastic anemia and toxic hepatitis There is no close relationship between toxic reactions and dose or duration of treatment, although fewer reactions occurred with smaller doses

Great precaution must be taken whenever this agent is administered *to patients. Each patient should be questioned regarding drug toxicity,* specifically, whether there is a past history of sensitivity to aminopyrine or to related drugs Phenylbutazone should not be administered if the history of sensitivity or intolerance to drugs of this group is positive or to several drugs of various groups The patient should be informed of the calculated *risk regarding toxicity before the drug is employed* The patient should be instructed to discontinue the medication should any new troubles be encountered and to report the development at once to his physician. The physician should prescribe sufficient medication for a three-day *initial trial* only. If the benefit over this period of time is not great, further administration should be abandoned. The smallest effective doses should be used Clinical observation of the patient by the physician should be made every *three or four days during the initial period of* drug administration. In addition to clinical scrutiny, a *blood count and urinalysis* should be ordered at regular intervals Even with each of these precautions, toxicity may develop No physician should prescribe this drug unless he is prepared to accept trouble from it at times. However, with careful clinical and laboratory control, toxic manifestations should be reduced in frequency and severity, so that serious consequences usually may be prevented. If toxicity is encountered or suspected, the drug should be discontinued, symptomatic

and supportive treatment should be vigorously employed and no further attempt should be made to administer the drug. The patient should be cautioned against ever ingesting the drug again.

SUMMARY

Phenylbutazone has been shown to be beneficial in various types of acute rheumatism, particularly to suppress and to relieve acute attacks of gout and bursitis. It may have great value particularly for patients who cannot tolerate other effective antirheumatic or analgesic drugs, which are ordinarily useful for such types of rheumatic disease. The physician should be thoroughly informed regarding the pharmacologic effects of this drug, its usefulness, the limitations of its therapeutic value, and especially its potential toxicity. With this knowledge of the drug, one should always consider its benefits as balanced against a calculated risk of toxicity. If it is administered, its use should be cautiously supervised in order that undesirable or side effects be minimized. Its use has been discussed also in acute rheumatic fever, traumatic arthritis and nonarticular rheumatic disorders

References

1 Van Riper, H E. Personal communication
2 Domenjoz, R Some pharmacological aspects of phenylbutazone (Butazolidin) a new antirheumatic Internat Rec Med *165* 467 1952
3 Wilhelmi, G and Domenjoz, R Vergleicheude Untersuchungen uber die Wirkung von Pyrazolen und Antihistaminen bei verscheidenen arten der experimentallen Entzündung Arch internat pharmacodyn 85 129 1951
4 Wilkinson, E L and Brown, H The effect of Butazolidin (phenylbutazone) on water and electrolyte excretion Am J M Sc *225* 153, 1953
5 Brodie, B B et al Observations on the antirheumatic and physiological effects of phenylbutazone (Butazolidin) and some comparisons with cortisone Am J Med *16* 181, 1954
6. Yü, T F, Sirota, J H and Gutman, A B Effect of phenylbutazone (3, 5 dioxo 1 2 diphenyl-4-n butylpyrazolidine) on renal clearance of urate and other discrete renal function in gouty subjects J Clin Invest 32 1121 1953
7 Smyth, C J Current therapy of gout J A M A 152 1106 (July 18), 1953
8. Gutman, A B and Yü, T F Current principles of management in gout Am J Med *13* 744 1952
9 Kidd, E G, Boyce K C and Freyberg, R H Clinical studies of phenylbutazone (Butazolidin) and butapyrin (Irgapyrin) in rheumatoid arthritis, rheumatoid spondylitis and gout Ann Rheumat Dis. 12 20, 1953
10. Byron, C S and Orenstein, H R Clinical evaluation of phenylbutazone (Butazolidin), a new anti arthritis agent New York J Med 53 676 1953.
11 Kuzell, W C et al Phenylbutazone (Butazolidin) in gout Am J Med *16* 212, 1954.

12. Steinbrocker, O, Neustadt, D A. and Ehrlich, M Butazolidin in the treatment of gout M Clin North America *38*: 611, 1954
13 MacKnight, J C, Irby, R and Toone, E C · Phenylbutazone in management of rheumatoid arthritis, rheumatoid spondylitis and gouty arthritis Geriatrics *9*, 111, 1954
14 Johnson, H P et al · Effects of phenylbutazone in gout New England J Med *250* 665, 1954
15 Bauer, W and Singh, M M Management of gout New England J Med *256* 171 (Jan 24), 1957
16 Lockie, L M. Present-day treatment of gout Bull Rheumat Dis *6* 97 (Nov), 1955
17. Smyth, C J · Personal communication
18 Strazza, J A, Jr and Ressetar, M.· Clinical studies with phenylbutazone (Butazolidin) in the treatment of arthritis J M Soc. New Jersey *50*. 333, 1953
19 Fleming, J and Will, G The treatment of acute rheumatism with Butazolidin. Ann Rheumat Dis *12*. 95, 1933
20 Kuzell, W. C., Schaffarzick, R W, Nangler, W. E, Gaudin, G and Mankle, E A Phenylbutazone a further clinical evaluation. Arch Int Med *92* 646, 1953
21. Lajananine, P, Sulas, P and Brock, M · Sur 3 cas de rheumatisme articulaire aigu traites par le phenylbutazone Presse méd *61* 759, 1953
22 Frain, J B and Morris, J E: Clinical experience with phenylbutazone (Butazolidin) Winnepeg Clinic Quarterly (*in press*).
23 Smith, C H and Kunz, H G · Butazolidin in rheumatoid diseases J M Soc New Jersey *49* 306, 1952
24. McCormick, E W Phenylbutazone in general practice G P. *8* 53, 1953
25 Steinbrocker, O, Berkowitz, S, Ehrlich, M, Elkind, M and Carp, S · Phenylbutazone therapy of arthritis and other painful musculoskeletal disorders J A M A *150*. 1087 (Nov 15), 1952
26 Kelly, M Phenylbutazone, correspondence. Brit M J 2· 936 (Oct 24), 1953
27 Rechenberg, H K von Rheumatherapie mit Butazolidin Schweiz. med Wchnschr *83*· 159, 1953
28 Gimena, J Rodriquez San Pedro, J M and Llanos, L.· Butazolidina· Nuestra experiencia con este neuevo medicamento antirreumatico Boll Inst Patol Med *8* 129, 1953
29 Mauer, E F The toxic effects of phenylbutazone (Butazolidin). Review of the literature and report of the twenty third death following its use New England J Med *253*. 404 (Sep 8), 1955

The Hand in the Differential Diagnosis of Arthritis

by John W. Sigler and Dwight C. Ensign

WHEN A PATIENT HAS ARTHRITIS, a careful study of the hands may often tell an important story. The hands are frequently involved in degenerative joint disease (osteoarthritis), rheumatoid arthritis, gouty arthritis, and psoriatic arthritis Localization and general appearance of the affected joints may aid the physician in differentiating the exact type of arthritis present Therefore, it behooves each physician to pay particular attention to the hands when observing patients with joint symptoms.

DEGENERATIVE JOINT DISEASE

Degenerative joint disease (osteoarthritis, "wear and tear" arthritis) is usually found in patients beyond the age of 40. In general, there is equal sex distribution, although hand changes appear to be more common in women than in men. Hand involvement may be limited to a single joint, as after acute trauma (baseball finger) or may involve most of the terminal interphalangeal joints as part of a generalized or primary osteoarthritis (fig 1)



FIG 1 Primary osteoarthritis, terminal interphalangeal joints (Heberden's node formation)

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14 Johnson, H P et al Effects of phenylbutazone in gout New England J Med 250 665, 1954
15 Bauer, W and Singh, M M Management of gout New England J Med 256 171 (Jan. 24), 1957
16 Lockie, L M, Present day treatment of gout Bull Rheumat Dis 6: 97 (Nov), 1955
17 Smyth, C J Personal communication.
18 Strazza, J A, Jr. and Ressetar, M: Clinical studies with phenylbutazone (Butazolidin) in the treatment of arthritis J. M Soc New Jersey 50 333, 1953
19 Fleming, J and Will, G The treatment of acute rheumatism with Butazolidin Ann Rheumat Dis 12 95, 1933
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21 Lajananine, P, Sulas, P and Brock, M.: Sur 3 cas de rheumatisme articulaire aigu traites par le phenylbutazone Presse méd 61 759, 1953.
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23 Smith, C H and Kunz, H G: Butazolidin in rheumatoid diseases J M Soc New Jersey 49 306, 1952
24 McCormick, E W: Phenylbutazone in general practice. G. P. 8 53, 1953
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26 Kelly, M Phenylbutazone, correspondence Brit M J 2 936 (Oct 24), 1953
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FIG 1 Primary osteoarthritis, terminal interphalangeal joints (Heberden's node formation)



FIG 2 Osteoarthritis of proximal interphalangeal joints (Bouchard's nodes) and terminal interphalangeal joints (Heberden's nodes)

The joint changes may be insidious and practically asymptomatic, or there may be acute intermittent exacerbations of tenderness, redness and swelling. As the disease progresses, the joints are usually less tender, but the swelling increases until finally there is definite enlargement of the joint. When such degenerative changes occur in the terminal interphalangeal joints (by far the most common site among all of the joints of the hands), typical Heberden's node formation is the result The original account by Heberden in 1782, quoted below, is still as accurate a description as any that have been written subsequently

Digitorum Nodi

What are those little hard knobs, about the size of a small pea, which are frequently seen upon the fingers, particularly a little below the top, near the joint? They have no connexion with the gout, being found in persons who never had it, they continue for life, and being hardly ever attended with pain, or disposed to become sores, are rather unsightly, than inconvenient, though they must be some little hindrance to the free use of the fingers

Similar changes occurring in the proximal interphalangeal joints are referred to as Bouchard's nodes (fig 2). Other hand joints occasionally the site of similar changes, especially in women, are the carpometacarpal and metacarpophalangeal articulations of the thumb

Heberden's and Bouchard's nodes may become symptomatic with exces-



FIG 3 Large synovial cyst adjacent to terminal interphalangeal joint

sive stress and strain on the hands, but once the stress subsides they are usually asymptomatic Degenerative joint disease may occur in any of the small joints of the hands, but whatever the site a history of trauma should be sought for, and, of course, further trauma should be avoided

Synovial cysts (fig 3) may occur as precursors to Heberden's nodes, or may appear concomitantly in patients who have already developed Heberden's nodes The cyst is filled with clear or opalescent gelatinous or mucoid material and may communicate with the synovial space of the joint or may be independent of it Such cysts may subside spontaneously and leave no residual, they may gradually increase in size and become so painful as to require excision In other instances, the cyst may become smaller and more firm and eventually lead to typical Heberden's node formation

X-ray changes in osteoarthritis are fairly typical Figure 4 shows degenerative joint disease of the terminal joints In spite of these marked changes,



FIG 4 Osteoarthritis of terminal joints Note marginal osteophyte formation, narrowing of the joint space, eburnation and subchondral cyst formation (Although joint space is narrowed due to cartilage destruction there is no true bone ankylosis)

note the preservation of the joint space (This will be shown to be a differentiating point between rheumatoid arthritis and osteoarthritis later in the discussion.) These x-ray changes are characteristically an over-production of bone regional to the affected joint.

More marked changes are noted in figure 5. These films show both terminal interphalangeal (Heberden's nodes), and proximal interphalangeal involvement (Bouchard's nodes) and more marked joint destruction Note the abnormal deflection of the phalanges. Apparent in both figures 4 and 5 is evidence of subchondral cystic demineralization (more marked in figure 5 due to advanced changes). Similar cystic areas may appear in rheumatoid arthritis, and may even suggest gouty changes; however, the cortex is not eroded

RHEUMATOID ARTHRITIS

Rheumatoid arthritis is prone to show changes in the hands and fingers early in the course of the disease. In contradistinction to osteoarthritis, it



FIG. 5 Heberden's and Bouchard's nodes showing advanced changes Note large osteophytes and abnormal deflection of phalanges due to joint destruction

usually has its onset between the ages of 20 to 40 years with females predominating 3 to 1. Rheumatoid disease in children (Still's disease) will not be considered here, although many of the concepts presented are true for juvenile rheumatoid arthritis as well as for the adult variety. Often the first symptoms of rheumatoid arthritis are stiffness, soreness, mild swelling, increased heat and slight discoloration of the overlying skin of the involved joint. The hands are characteristically cold and clammy, occasionally warm and moist with reddening of the palms, especially in the thenar and hypothenar areas. The hand joints most frequently affected are the proximal inter-



FIG. 6 Early rheumatoid arthritis with typical "spindling" of the proximal interphalangeal joint, index finger.

phalangeal (fig. 6) and metacarpophalangeal joints (fig. 7). Symmetrical involvement is the rule, although very early in the course of the disease, one may find monarticular involvement. As the disease progresses, the joints become fusiformly enlarged and there is an increased synovial effusion. Again in contradistinction to osteoarthritis, a rheumatoid joint tends to have a spongy consistency when palpated, partly due to synovial thickening and partly due to joint effusion.

With further progression, the periarticular structures become more thickened with fibrotic changes, and the synovitis progresses with gradual



FIG 7 More advanced rheumatoid changes, involving the second and third metacarpophalangeal joints with early extension deformities in the proximal interphalangeal joints Note early muscle atrophy over the dorsum of the hand

cartilage destruction from pannus formation. With these *changes there is abnormal joint deflection produced by the combination of muscle atrophy and* intra-articular damage. Note ulnar deviation of the digits *at the metacarpo*-phalangeal level in figure 8 and muscle atrophy of the dorsum of the hand

In any stage of the disease, rheumatoid nodules may develop over the *bony* prominences. Figure 9 shows multiple rheumatoid nodules over the small joints of the hands. Later, if the disease progresses, one may see flexion and extension contractures, excessive muscle wasting, and increased ulnar



FIG. 8 Rheumatoid arthritis showing early abnormal ulnar deflection of the digits at the metacarpophalangeal joints

deflection at the metacarpophalangeal level (fig 10). An occasional rheumatoid patient will develop marked bone absorption leading to the so-called "opera glass hand" deformity. The fingers are literally telescoped due to lack of the supporting bone structure (fig 11).

X-ray changes in early rheumatoid arthritis are only slight. In the earliest phase, only soft tissue swelling may be apparent (fig. 12); later, slight subchondral osteoporosis is noted (fig 13). As the disease progresses, the bone changes become more marked with narrowing of the joint space,



FIG 9 More advanced rheumatoid changes Note multiple rheumatoid nodules over thumb and metacarpophalangeal joints

more marked subchondral cystic changes, subluxations and abnormal joint deflections (figs 14 and 15). In advanced rheumatoid arthritis x rays will show marked osteoporosis, continued cartilage destruction and, in some far-advanced cases, actual bony ankylosis (fig. 16). Figure 17 shows the x-ray of the "opera-glass hand" in figure 12.



FIG 10 Marked hand deformities due to rheumatoid arthritis

It should be mentioned that both osteoarthritic and rheumatoid changes may be found in the same individual, particularly in the later decades, but that in contradistinction to rheumatoid arthritis, bony ankylosis never occurs in osteoarthritis.

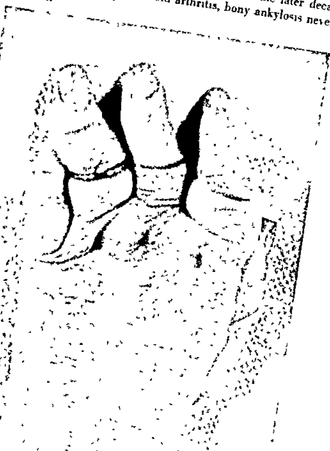


Fig 11 "Opera glass hand" deformities of rheumatoid arthritis

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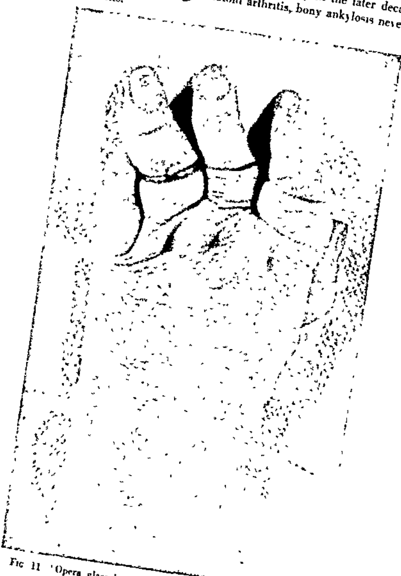


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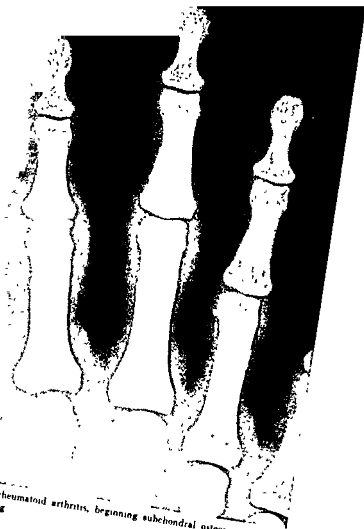
GOUTY ARTHRITIS

Gout is a common but frequently overlooked disease Many patients with this metabolic defect develop gouty arthritis Gouty arthritis may occur at any age and it may affect any joint. While involvement of the great toe is



Fig 12 Early rheumatoid arthritis with soft tissue swelling of the interphalangeal joints

most frequently noted, fifty per cent of attacks of gout occur in other joints. Next in frequency to the great toe, attacks occur in the elbows, tarsus, ankles and knees. Gout is not infrequently seen over the dorsum of the hand and may involve the small joints of the hand: Metacarpophalangeal (fig 18), proximal interphalangeal, terminal interphalangeal Gout occurs more



13. Early rheumatoid arthritis, beginning subchondral osteoporosis and slight ce narrowing

commonly in men than women in a ratio of 20 to 1. It is much more frequent in white patients than colored, but it does occur in colored occasionally and it has occurred in colored females.

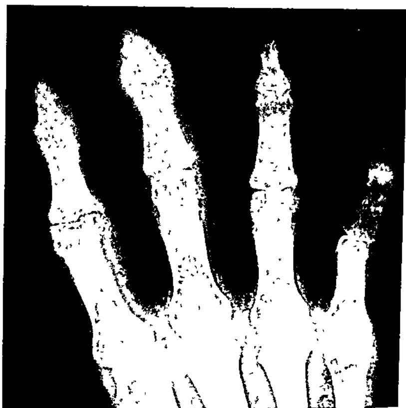


FIG 14 Rheumatoid arthritis with marked osteoporosis and subchondral cystic changes

Attacks of acute gouty arthritis may develop very rapidly; the joint becomes dusky red, hot, swollen and exquisitely tender. Any such acute joint involvement in a hand joint, particularly in a middle-aged male, should be considered gout until proved otherwise, just as would be the case for similar involvement in the great toe; a therapeutic test with colchicine often makes the diagnosis certain.

Acute gouty arthritis subsides leaving no residual joint changes. However, after recurrent attacks and when no effort is made to control the tissue urate levels, chronic tophaceous gout may occur. Tophi (deposits of sodium monourate crystals) may occur in any tissue of the body, the more obvious being in bone and subcutaneous or superficial layers of the skin. At times

these tophi discharge a white chalky material. Not as obvious are the changes in figure 19. This patient has mild degenerative joint disease, but in addition, tophaceous gout involving the third terminal interphalangeal joint. Figure 20 shows typical x-ray changes with punched-out areas of bone adjacent to the involved joint in this patient.



FIG. 15 Rheumatoid arthritis with extension deformities of third and fourth proximal interphalangeal joints. Note extensive destruction of these joints

Larger deposits of urates in the bones and soft tissues of the hands are seen in figure 21 It is hoped that in the future these changes can be prevented with the use of uricosuric agents such as Benemid and the careful management of these patients It must be stressed that gouty arthritis is a common disease and the practicing physician must have a high index of suspicion for it if the diagnosis is to be made. In suspected cases, high serum uric acid may be found although one may be misled in an occasional case by normal serum uric acid levels

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FIG. 14 Rheumatoid arthritis with marked osteoporosis and subchondral cystic changes

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arthritis never occurs in the terminal interphalangeal joints, whereas this represents a commonplace occurrence in patients with psoriatic arthritis



FIG 17 Rheumatoid arthritis with "Opera glass hand" deformity (see fig 12) Note bone absorption in all areas, often referred to as "arthritis mutilans"

Arthritis due to psoriasis usually occurs in patients with long-standing psoriasis Joint symptoms may occur, however, in any stage of the disease Figure 22 shows typical psoriatic nail involvement with characteristic pitting, but only minimal involvement of the terminal interphalangeal joint of one finger. Figure 23 shows nail changes and enlargement of the terminal interphalangeal joints The enlargement in these joints is along the lateral margins, and the dorsum of the joint is flattened, differing in this respect from the appearance of Heberden's nodes in osteoarthritis (compare fig 1). Occasionally the proximal interphalangeal joints may be affected (fig 21).



Fig. 16 Rheumatoid arthritis with bony ankylosis of the second and third proximal interphalangeal joints

PSORIATIC ARTHRITIS

Arthritis is frequently seen in patients with psoriasis Whether the type of arthritis is the same as rheumatoid or whether it is a separate entity is still subject for debate It is axiomatic, however, that typical rheumatoid



Fig. 19 "Mixed arthritis," osteoarthritis and tophaceous gout of the third terminal interphalangeal joint (see fig. 20)

ful search should be made by history and by examination for evidence of psoriasis.

MISCELLANEOUS LESIONS OF THE HAND

It would be unpractical to consider all the swellings in and adjacent to the joints and tendons which at first glance may suggest arthritis. However,



FIG 18 Gouty arthritis Note swelling of second metacarpophalangeal joint

The joint changes tend to progress in the same manner as rheumatoid joints, although there is apt to be more bone destruction. X-ray changes are mild in early psoriatic arthritis, but as the disease progresses there is bone destruction about the involved joints (fig. 25). In more advanced disease there is marked absorption of the head ("pencilling") and in some cases of the shaft of the involved bone. Figure 26 shows very advanced changes. In any patient with atypical joint involvement in the hands or elsewhere a care-



Fig 21 Tophaceous gout with multiple tophus formations

the fingers into flexion toward the palm of the hand, associated with ing of the skin of the palm Nodular thickening in the palm is appar ring finger is most commonly involved, next the little finger, then th finger and then the index finger. The thumb is seldom affected



FIG 20 Gouty arthritis with tophaceous deposits adjacent to terminal joint

some of the more common ones will be mentioned briefly in the following

Ganglion A ganglion is a common type of swelling that may occur in any tendon sheath or joint capsule It frequently occurs over the dorsum of the wrist (fig 27). It is a cystic swelling of the tendon sheath, the exact cause of which is unknown. It is often associated with trauma and has especially high incidence in a pianist, typist, etc

Dupuytren's Contracture. Dupuytren's contracture (fig 28) results from a progressive thickening of the palmar fascia which, as it contracts, pulls



Fig 21 Tophaceous gout with multiple tophus formations.

the fingers into flexion toward the palm of the hand, associated with puckering of the skin of the palm. Nodular thickening in the palm is apparent The ring finger is most commonly involved, next the little finger, then the middle finger and then the index finger. The thumb is seldom affected. In early

cases the nodular thickening of the palmar fascia may resemble a subcutaneous nodule of rheumatoid arthritis, but the joints themselves are not involved. The condition is often misdiagnosed as arthritis.

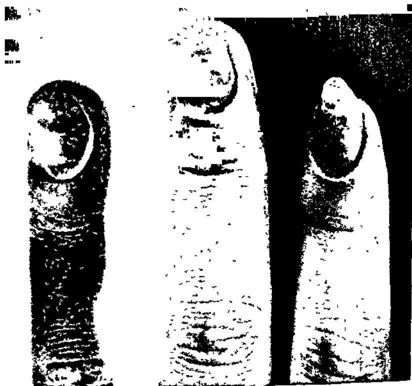


FIG 22 Early nail changes (pitting) in psoriatic arthritis

Knuckle Pads. Knuckle pads (fig. 29) are rather uncommonly seen; they are located over the dorsal aspect of proximal interphalangeal joints and at first glance may suggest rheumatoid arthritis. However, these pads are purely soft tissue thickening and bear no relationship to joint disease. They are usually asymptomatic and interfere only slightly if at all with flexion of the fingers They may occur in early life, or occasionally past middle age, and there is usually no occupational etiology. There may be some kinship with Dupuytren's contracture, inasmuch as both types of lesions appear in some individuals.

Xanthoma Xanthomas may occur in any joint, tendon sheath or other tissues, however, a commonplace site is in tendon sheaths of the hand (fig 30). The tumor is firm, and may be smooth or irregular. The primary etiology of these tumors is an alteration in fat metabolism.

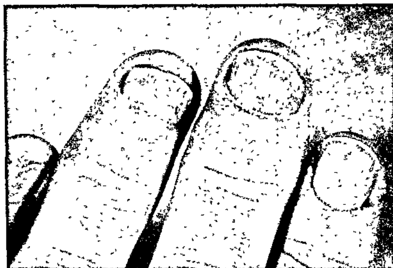


FIG 23 Psoriatic arthritis with typical nail and adjacent terminal interphalangeal joint involvement

Needless to say, many other abnormal swellings may appear about the hand Most are benign, but malignant tumors may occur

This brief and superficial description of some of the manifestations of arthritis in the hands is presented in the hope that it may arouse interest in a group of diseases frequently neglected in their early stages. Each time a physician sees a patient, he sees that patient's hands If those hands suggest that arthritis is present, prompt and thorough follow-up may spare the individual much suffering and disability.



FIG. 24 Psoriatic arthritis with involvement of the proximal interphalangeal joint of the index finger, as well as the second, third and fourth terminal joints.



FIG 25 Early x ray changes in psoriatic arthritis Note eburnation of bone and early joint space narrowing of third terminal joint



FIG 26 Advanced psoriatic arthritis with diffuse resorptive changes causing so-called "pencil in cup" deformity—particularly marked at fourth metacarpophalangeal articulation



Fig 27 Ganglion Dorsum of the wrist



FIG 28 Dupuytren's contracture showing moderate contracture of the palmar fascia



Fig 29 Knuckle pads



Fig 30 Xanthomas regional to the metacarpophalangeal joints

Medico-Legal Aspects of Trauma to the Joints and the Spine

by Paul D. Williams (L L.B.) and L. Maxwell Lockie

THERE IS A PAUCITY OF REPORTS concerning the medico-legal aspect of trauma as it affects arthritis and other conditions of the bones and joints During the past twenty years the authors have had considerable court experience representing both plaintiff and defendant—and not always on the same side It stands to reason therefore that the opinions expressed herein are on an impartial basis Our aim is to set forth the results of these experiences in order to aid in the proper adjudication of the problems with respect to duration of disability, as influenced by trauma

TRAUMA TO PREVIOUSLY NORMAL JOINTS

It is not necessary to dwell upon trauma that might be classified as proved injury to previously normal joints. Whenever a case involving fractures is encountered, established by x-ray or otherwise, in joints or bones previously known to be normal, it is reasonable to assume that the referee or jury has no choice but to establish the loss of use, if any, in dollar value Generally speaking, the medico legal point of view is concerned with the disability remaining after injury It should be stressed that there is a marked difference between disability and distress Disability may be defined as an impairment of the ability to work or to use a part of the body while distress, on the other hand, need not per se be severe enough to constitute a disability.

Among the most troublesome injuries to previously normal joints are those involving fractures of the heel, the wrist, the forearm and the elbow When such injuries occur to a mechanic, a workman in the building trades, or a machinist in a machine shop, grave impairment of earning capacity may be involved. A state medical examiner, who reports upon a case to a compensation board, is given rather wide latitude in the establishment of the permanency of any injury It is observed frequently that his findings take into consideration the actual embarrassment to the patient's earning capacity in a specific occupation Moreover, a similar disability in another person in a different occupation might be established as either an increased or a decreased loss For example, if a painter suffers a fractured os calcis, there may be residual inability to paint and to decorate while standing on the rungs of a ladder If a carpenter suffers a severe and perhaps displaced

fracture of the wrist or elbow he may be unable to use hand tools, with consequent severe impairment of *his capacity to continue* in that type of work.

It is recognized that trauma to a joint may involve soft tissues and other *parts which do not reveal* x-ray evidence of injury. Injuries of bony tissue, soft tissue and connective tissue are of equal concern and, in each instance, enter into the evaluation of the degree of ability. Too frequently, the physician who comes irregularly to the law courts confuses the elements of pain, suffering, complaints of distress and other subjective matters with the essence of the problem, which is the question of *disability*. Disability, as such, is the core or the basis of the demand for monetary damages

TRAUMA IN OSTEOARTHRITIS

Peripheral Osteoarthritis

Complex questions particularly arise in cases of osteoarthritis where, *prior to injury, there is no proof of disability, either by history or documentation*, in the traumatized osteoarthritic joint. The question of aggravation to the underlying osteoarthritic process is pertinent to the discussion if the matter is subject to litigation, since it is widely known that opinions are expressed to the effect that the period of aggravation continues for from one week to several years It would seem to be a wise policy for the medical profession, generally, to establish a reasonable formula that might be applied to the majority of such cases, inasmuch as insurance rates and other similar factors depend largely *upon loss of experience*. There would be a tremendous value, from a socio-economic as well as a medico-legal point of view, to have such losses due to aggravation more or less circumscribed by a formula *No pattern, of course, could encompass all types of such cases, but if there* is evidence established that an underlying disease process did exist prior to injury, perhaps a rule involving common principles could be attached to the period of the so-called aggravation or precipitation of symptoms *For* example, in cases where objective evidence of aggravation, including such factors as limited motion, swelling and spasm, has disappeared, and the remaining residual comprises subjective complaints, a period of two months of causally connected disability on the basis of aggravation would seem entirely adequate

In cases where an established pre-existing osteoarthritis is accepted with distress or disability of some character prior to the injury *to the joint*, *the period of disability following* injury is ordinarily much less, as determined by a referee or a jury, than in cases where previous distress or disability was not established The court and jury is relatively medically realistic in the face of an *admission of disability prior to injury*.

Osteoarthritis of the Spine

What has been stated with respect to osteoarthritis in peripheral joints is magnified considerably in cases of back injury. Statistically, cases of back injury involved in litigation are far more expensive in money and time lost than are the cases seen privately, where the element of gain does not exist. Few individuals who suffer back injury admit distress or disability in their back prior to the accident or incident, despite x ray evidence of osteoarthritis of the spine prior to injury or immediately thereafter X-ray findings of the presence of bone changes characteristic of osteoarthritis prior to the injury, or the demonstration of progression following the injury as seen in the normal anticipated development of the disease process, is proof of pre-existing arthritis It has been our experience that numerous claims are made concerning the spine with respect to relatively profound aggravation and pain. At this site, more than in any other region, a rational and practical formula is needed for the assessment of a reasonable period of causally related aggravation This is certainly preferable to permitting the continuance of widely varying opinions concerning permanency of the aggravation.

When extensive osteoarthritic involvement of the spine is demonstrated, upon which is superimposed severe injury resulting from a concededly serious accident (e.g, a fall from a high place) involving the mechanics of compression, and in the absence of demonstrable x-ray evidence of change when the distress and disability are consistent with the commonly accepted pattern of complaints, it is impossible to establish a maximum period for the ensuing aggravation It will be noted, however, that in this class of cases to establish protracted aggravation the patient must display symptoms in keeping with a reasonable classic pattern of disability consistent with medical experience as it pertains to osteoarthritis of the spine. The matter of exaggeration must always be considered. Typically, it may be expressed by the patient when he claims to be suffering excruciating pain, even though there is no motion of the spine to initiate pain, e g, when he is seated, at rest or lying down. Complaints of pain on a high level, continuous and unremitting, are not consistent with this disease process. It is the clinical observation of one of us (L.M L.) that osteoarthritis is accompanied by a characteristic pain pattern, which may extend from the absence of pain to maximum pain, depending upon circumstances that involve posture and motion by the patient at that time.

The next class of case includes the patient with pre-existing osteoarthritis who becomes involved in a trivial incident. Such a patient, as the result of for example reaching down to pick up an object as small as a pencil from the floor or turning to place material on a table behind him, alleges the

onset of excruciating pain of prolonged duration, on the basis of a back strain. There is no evidence of severe trauma to the patient; if direct joint *injury has not been claimed and there has been* no aggravation of the under lying osteoarthritis, it must be assumed that injury, if it has been sustained, has been confined to soft tissues. Although these cases are diagnostic chal *lenges to the examining* physician, it is admitted readily that soft tissues heal relatively rapidly at all ages It is submitted, therefore, that the dura tion of aggravation should not exceed a period of 12 weeks. This observation does not apply, of course, in cases where examination reveals evidence of nerve root damage or the intervertebral disc appears to have been injured

It is our experience that the spine and injuries thereto constitute a most important and difficult problem, both to the insurance industry and to the courts. The reason for this, although often obscure to the physician, is readily apparent to the lawyer: the legislatures of many states have provided liquidated sums of money for total or partial losses of fingers, toes, hands, arms, legs, eyes, etc., and for the loss of use of these members In reference to back disability or injury, however, there is seldom a maximum liquidated figure that can be anticipated Injuries to the back are almost unlimited in terms of dollars Because a large percentage of all injuries relate to the back, any effort to clarify some of the critical problems on an impartial basis is commendable. Again, it must be remembered that aggravation should be determined by *evidence of disability, not by distress alone.*

THE LOW BACK INJURY

It is most significant that a large percentage of the protracted disabilities seen in the compensation courts involve a relatively small region of the entire human body. The area *in reference lies between the third lumbar vertebra* and the *first sacral segment* of the spine Orthopedists, generally, have commented upon the preponderance of injuries which involve lifting and falling, *the dire effects of which so frequently are confined to this portion* of the vertebral column It is appreciated that this area may be the focal point of osteoarthritis, degenerative intervertebral disc disease, protruded *intervertebral discs, spondylolisthesis and sacralization of* the transverse processes of the lowest lumbar vertebra on the sacrum, each of which may be accompanied by pain and may lead to disability in varying degrees for varying periods of *time Spondylolisthesis is referred* to specifically below. It is evident that the examining physician must appraise the problems of this area carefully with regard to differential diagnosis, which requires repeated x-ray *examination and certain laboratory* data, in addition to the history and physical examination. The clinical history, since it may be the most important element establishing the correct diagnosis, must be recorded *in detail.*

RHEUMATOID ARTHRITIS

Rheumatoid arthritis is a constitutional, connective tissue disease of unknown origin. It may occur at any age, but the onset is most common between the ages of 35 and 55 years. The malady affects females in the ratio of 3 to 1. The onset is insidious, accompanied by fatigue, loss of weight, loss of appetite and often fever. There are many laboratory studies which may be abnormal, although no single test as yet is specific for this type of arthritis.

Any joint may be involved. However, the physician may be reasonably positive of the diagnosis of rheumatoid arthritis if one or more of the following sites are affected:

(1) The proximal interphalangeal joints, with increased capsular thickening and increased fluid formation.
(2) The metacarpal phalangeal joints, with swelling and limitation of motion.
(3) The ulnar aspect of the wrists, with pain and swelling.
(4) The elbows, with incomplete extension when not caused by injury or by gouty arthritis.
(5) Demonstrable fluid in the knee joints with or without limitation of normal range of motion, especially extension.

Treatment consists of adherence to a well rounded program suited to each individual. This requires a careful survey in order to determine the best plan of management. The patient must be convinced that it is beneficial to follow the program and to understand the details thoroughly as they should be executed. The important facets in therapy consist of:

(1) Complete bed rest for three weeks, preferably in a hospital; followed by modified rest until the activity of the disease subsides. This latter phase may require several months of careful and patient direction.
(2) Administration of weekly intervals of gold salts, such as gold sodium thiomalate (Myochrysine) intramuscularly for a prolonged period.
(3) Instruction in physical therapy by a competent physical therapist. This embraces the use of heat and exercises.
(4) The proper administration of adrenal corticosteroids or ACTH, as necessary.
(5) Administration of analgesics such as salicylates for relief of pain.
(6) Detailed instruction and supervision to prevent deformities, especially of the hands, back, knees and feet.
(7) Directions concerning proper mattresses, chairs and posture.

(8) Psychotherapy and reassurance throughout the entire time the patient is under the care of the physician.

A most difficult problem arises when the patient with rheumatoid arthritis suffers an injury to a single joint, such as the knee joint, followed by persistent swelling and disability in the affected area. As time passes, other joints may be involved in a typical picture of rheumatoid arthritis. In such a situation, which one of us (L.M L.) has discussed with other rheumatologists, it is believed that the carrier should be responsible for the injured joint only for a period of one year. It is also his opinion that the disease is not caused by injury but would have occurred at that approximate time, for the reason that there are constitutional manifestations which are so widespread that it is difficult to ascribe them to an injury. The actual number of these cases in the courts is small

When a minor injury befalls a well established rheumatoid joint, the aggravation, as the result of strain or mild trauma, usually produces an exacerbation of activity of the affected joint for a period varying from two to six months. It matters little whether an underlying susceptibility is present in the patient or not; if any injury sets the stage for infection and infection is followed by localization in one or more joints, the original injury or accident is chargeable with the end consequences

A more serious problem appears in cases in which the injury is followed within a relatively short time by typical rheumatoid arthritis. Most opinions in the past concerning casual relationship in such cases rest upon the theory of reduced natural resistance of the traumatized part Although a single such opinion is contradicted by physicians well versed in the field, any opinion, especially by the family physician, of causal relation usually is seized upon and a verdict for the patient may follow. This factor is important in the adjudication of the problem based upon the weight of medical evidence.

RHEUMATOID SPONDYLITIS

This syndrome is identified also as Marie-Strümpell arthritis. The onset of the disease is insidious. It occurs usually in young men Approximately ten per cent of the cases are in females The initial symptom frequently is pain with persistent discomfort in the low back. Even at the time of the earliest complaints, an x-ray of the sacroiliac joints reveals bilateral sclerosis with narrowing of the joint spaces This roentgenographic finding is so characteristic of the disease that only a few cases are reported in which it is absent. As the condition progresses, there may be an increasing stiffness of the spine, which results in the characteristic poker spine. A number of years later, there may be marked forward bending of the spine with permanent deformity. As the spinal involvement continues, arthritis of the costal-vertebral joints may appear with absence of chest expansion due to failure of the ribs to ele-

vate on inspiration Later there may be involvement of the two large pairs of joints, the shoulders and hips If the process continues without interruption, peripheral joints will be swollen, painful and restricted in motion, as in peripheral rheumatoid arthritis In extremely active cases, constitutional symptoms of fatigue and weight loss are expected. The only laboratory datum consistently abnormal is an increased sedimentation rate. Curiously and without known cause, progression in this type of arthritis may cease at any time.

Treatment consists of a program which involves strict attention to posture and consists of regular periods of deep breathing, the use of a firm mattress in the bed and proper chairs, such as straight-backed or occasional chairs. At no time is the patient permitted to sit in a lounging chair or a sofa. In many patients the wearing of a modified Taylor-type back brace is necessary to preserve posture The prognosis is dependent to a great extent upon the preservation of good posture. Phenylbutazone (Butazolidin) frequently gives great symptomatic relief and seems more beneficial than aspirin or other forms of salicylates in this type of arthritis The dosage of not more than 300 mg per day lessens the danger of a serious reaction to the drug. X-ray therapy over painful areas of the spine frequently produces excellent pain relief. Gold therapy is ineffective.

Injury occurring in a person with this type of arthritis, which involves a fall from a height or trauma of force to the back, may aggravate symptoms for months. Recovery to the preinjury status is slow and in many cases there remains some permanent partial disability. Minor strains, such as result from bending over to pick up objects or twisting the back in an unguarded manner, may initiate symptoms lasting from two to three months

PAGET'S DISEASE

Generally, trauma is not considered to be the cause of generalized Paget's disease However, instances are encountered in which injury to a particular bone is described, followed by a diagnosis of Paget's disease. In such exceptional cases, in the absence of a more definitive appraisal of the disease process, it is likely that a verdict favorable to the plaintiff will follow in court. Systemic study of the entire skeleton by x-ray is indicated where such a claim is made, and if the osteitis deformans is detected elsewhere, the finding of Paget's disease in the part traumatized is usually considered to be coincidental On the other hand, if localized changes of Paget's disease are present in a patient who has experienced a relatively trivial injury, it may well be anticipated that the injury will be charged with contribution to a pathologic fracture and its sequelae It is fortunate that the incidence of Paget's disease is low, because of the notion and legal fact that industry accepts employees as they are Few cases are seen with serious consequences of

relatively trivial trauma superimposed upon pre-existing osteitis Perhaps a reasonable test in cases of this sort would be to require definite evidence of injury to the bone affected with further proof that the disease is limited to the bone traumatized. X-rays taken at the time of injury are irrefutable and it must be supposed that the disease will be apparent within the period that ordinarily would be required to restore the damaged tissues

SPONDYLOLISTHESIS

Relatively few persons are diagnosed as having this congenital anomaly, unless by accident during a routine x-ray study. It seldom is the cause of disability. *The condition, however, becomes of immense importance coupled as it frequently is with back strain and other spinal injuries, when it is diagnosed by x-ray Some physicians are apt to make the mistake of advising their patients of the existence of this condition—a condition found coincidentally while the patient is undergoing treatment of other back injuries.* It seems to do little good to advise a patient that he has a congenital, unstable back, when the first knowledge of it comes with a back injury. In the relatively large numbers of patients seen in litigation with this finding, the existence of the condition complicates significantly the restoration of the patient to his pre-accident status

CONCLUSION

It should be possible, after a careful study, to determine with reasonable accuracy the period of disability as the result of injury concerning arthritis and other disturbances of the bones and joints.

Selected Bibliography

1 Reed, J V and Emerson, C. P - The Relation Between Injury and Disease Indianapolis, Bobbs-Merrill, 1938
2 Spicer, F W [illegible] 1939.
3 Brahdy, L. and [illegible] er, 1937
4 Stern, R A - [illegible] 1945

Induced Connective Tissue Syndromes

by Fred B. Rogers and John Lansbury

FROM THE STANDPOINT of differential diagnosis and practical clinical management, *it is important to recognize the increasingly common occurrence of* drug-induced syndromes which mimic and in some instances almost duplicate certain connective tissue diseases In most of these "induced syndromes" [illegible] the treatment consists mainly of withdrawing [illegible] set in motion Perhaps of even greater importance is the possibility of artificially producing *in animals certain "rheumatic" or "collagen" syndromes* which closely resemble the naturally occurring human diseases. The tremendous advantages of being able to study the disturbed physiology in such animals with the hope of applying the findings to human disease are obvious.

Many attempts have been made to reproduce a variety of connective tissue disorders in animals In an effort to relate these disorders to human disease, we must bear in mind that they appear to be incomplete syndromes *which resemble but do not exactly duplicate their human counterparts Also,* in the case of human disease, there is a great deal of overlapping in both the histologic and clinical pictures of the various "collagen" diseases This calls for additional caution in attempting to equate the induced syndromes in animals with human disease

DRUG AND SERUM INDUCED ARTHRITIS

In the case of rheumatoid arthritis, it is well known that acute, subacute and chronic joint inflammation can be induced in animals by a variety of quite different techniques, such as the violent hormonal manipulations of Selye, the intraarticular injection of bacterial products in an animal previously sensitized to the same antigen, or infection with live pleuropneumonia-like organisms Yet, no one seriously believes that such animals are *really* suffering from life-long, progressive and crippling rheumatoid arthritis Indeed, it may be argued that rheumatoid arthritis is a species-specific disease which, therefore, can only exist in humans and that the experimental animals are, so to speak doing their best within the limitations imposed on them by their specific constitution to develop rheumatoid arthritis If this is true, the most that can be hoped *for is that some of the mechanisms involved in the* induced arthritides may parallel those encountered in spontaneous human dis-

ease and so lend themselves to controlled study. Much the same situation is obtained when we try to interpret the important work of Rich and Gregory in connection with the experimental production of lesions resembling those of rheumatic fever.[1] Because affected animals do not develop life long, recurrent episodes of valvulitis ending in scarring, deformity and bouts of congestive failure they cannot be said to "have" rheumatic fever. Nevertheless, some common mechanisms *may be operative in both the animal and human* syndromes.

In the case of osteoarthritis the situation again is much the same. Cartilage degeneration and bony proliferation have been produced in animals by aminonitriles derived from sweet peas. The resulting lesions, however, do not in all respects resemble the naturally occurring osteoarthritis of humans.

Since attempts to reproduce the various arthritides in animals have so far failed to explain the pathogenesis of these diseases in humans, we may now inquire into the possibility of inducing these *syndromes in humans* themselves

In humans, transient but very definite joint inflammation has been described during the administration of iodides, heavy metals, and a variety *of drugs*, but *none* of these induced syndromes bears more than a superficial resemblance to spontaneously occurring human arthritis.[2] In the case of sulfonamides, the picture is different. There appears to be a relationship between sulfonamide-treated infections and polyarteritis *nodosa, and* in "sulfatoxic arthritis" and penicillin reactions the clinical picture still more closely resembles the "collagen" diseases Serum sickness perhaps comes closest of all to reproducing the acute phase of collagen diseases, *since it* causes widespread alterations in serous membranes, *serum* proteins, kidneys, blood vessels and joints and even the L. E. cell phenomenon.

These reactions to drugs and serum appear to *involve a disturbance* in the basic immunity mechanism, and it is tempting *to assume* that the *spontaneously arising* collagen diseases have a similar etiology. However, *it has not so far been possible to demonstrate that the rheumatic diseases are* primarily due to an antigen-antibody reaction *Indeed, the recent* observation of what appears to be rheumatoid arthritis in cases of *agammaglobulinemia suggests* that the disturbances in immunity may be a result of the rheumatoid process rather than its cause.

THE HYDRALAZINE SYNDROME

To the above list of "induced syndromes" there has recently *been added* another that is of extraordinary interest. We refer to the side *effects* which have been observed after prolonged administration *of Apresoline* (hydralazine hydrochloride) to *patients suffering* from *arterial hypertension*. This *reaction*, termed the "Hydralazine Syndrome,"[3] has been *reported* in 7-10

per cent of patients given an average of 600 mg. or more of this drug dai over periods longer than eight months. In most instances the syndron developed when the diastolic pressure had fallen to normal levels; in som cases it seemed to be precipitated by the development of an intercurren infection. Initially there may be chills and migrating pains in the muscles and joints. Later there is symmetrical arthritic involvement of the proximal interphalangeal joints and a clinical picture resembling rheumatoid arthritis. If hydralazine was continued, fever often developed and was accompanied by prostration, pleural, pericardial and joint effusions, and erythematous skin eruptions resembling those seen in systemic lupus erythematosus. In addition, sensitivity of the skin to ultraviolet light, lymphadenopathy and splenomegaly have been noted. Histologically, abnormal collagen has been seen in muscle and skin. In one instance a typical rheumatoid nodule was described,[4] and in another lymphorrhea in muscle resembled that of rheumatoid arthritis. There may be a decrease in serum albumin concentration and increase in alpha and gamma globulins. The sedimentation rate was usually elevated, and occasionally a false positive serologic test for syphilis was found, as well as anemia and leukopenia. In a few cases L. E. cells were found in the peripheral blood and bone marrow.

Taken together, the main features of the hydralazine syndrome closely parallel the clinical, serologic and histologic picture associated with active collagen disease, particularly disseminated lupus erythematosus.[5] It should be emphasized, however, that only a few of the patients have developed this complete picture which resembles the clinical manifestations of disseminated lupus erythematosus. It has been pointed out, however, that there are certain differences between this drug-induced syndrome and spontaneously occurring systemic lupus. The hydralazine syndrome has been noted predominantly in males. There has also been a paucity of urinary abnormalities, such as hematuria, cylindruria or proteinuria. In its reversibility and the relative infrequency of L. E. cells and renal manifestations, the hydralazine syndrome therefore deviates from spontaneously occurring lupus erythematosus disseminatus.[6]

In general, the syndrome subsides when the drug is withdrawn. In a number of instances it has been reactivated by re-administration of hydralazine. Occasionally the manifestations persist after the drug has been discontinued and in these circumstances can be suppressed by steroid therapy. This suggests that in a few instances the patient had systemic lupus erythematosus when hydralazine therapy was begun. It seems unlikely, however, that 10 per cent of these hypertensive patients could also have had a latent form of rheumatoid arthritis or systemic lupus at the time therapy was instituted.[7] Most observers do not consider this syndrome an allergic or sensitization

reaction to hydralazine, since its onset and severity are related to the total dosage and length of administration of the drug. These relationships are more consistent with the possibility that there is a progressive depletion of some substance of physiologic importance. As a chemical, hydralazine hydrochloride combines with carbonyl and sulfhydryl radicals and has a strong affinity for metallic ions. This chelating effect may result in the creation of a trace-element deficiency related to interference with certain enzyme systems There is now experimental evidence to support this possibility. Comens[8] has recently reported the experimental production in dogs of a disease possessing clinical and pathologic similarities to systemic lupus erythematosus. This syndrome followed oral administration of hydralazine to dogs for one to eight months in dosages similar to those used in man The L. E. cell phenomenon, however, has been demonstrated with serum from these dogs

EXPERIMENTAL HYDRALAZINE DISEASE

In a subsequent experiment,[9] hydralazine was given to 10-day-old cockerels, all of which developed perosis within six weeks, a disease believed to be the result of manganese deficiency. (Perosis, a term derived from the Greek word meaning maimed or disabled, is a nutritional disorder of young chicks and turkeys. Also called "hock disease," it is characterized by shortening and thickening of the limb bones and a deformity known as "slipped tendon." Perosis is associated with a high intake of inorganic phosphate or calcium salts and low intake of manganese. Manganese, biotin and choline may prevent the bone deformities.) Another group of cockerels fed hydralazine and manganese citrate 5 mg per day, simultaneously, developed normally

Comens has found that manganese inhibits the in vitro formation of the L. E. cell in the blood of patients with systemic lupus erythematosus in a concentration of 1×10^{-3} molar. Copper, cobalt, zinc and iron caused no such inhibition. All of the dogs fed hydralazine alone developed a lupus-like syndrome, but no glomerular wire-loops were found in the kidneys of two dogs given manganese citrate parenterally Three patients with the hydralazine syndrome and two with systemic lupus were reported to have improved symptomatically when the manganese ion was administered orally.[10] Comens suggests that hydralazine may produce the hydralazine syndrome by binding manganese ions, thus possibly blocking certain dependent enzyme systems Extensive research is now in progress on this intriguing problem

CONCLUSION

In summary, it seems that through hydralazine, for the first time, the "rheumatic state" can be reproduced both in man and in experimental animals Hydralazine is thus unique in this respect. Already there is evidence that the induced syndrome can be prevented and reversed by the

administration of small doses of manganese. (The presumed enzyme-blocking action of gold in cases of rheumatoid arthritis suggests a somewhat parallel situation). But the important question remains, "What is the relation between the hydralazine syndrome, subacute disseminated lupus erythematosus and rheumatoid arthritis?" To claim that the three are identical would be, we believe, unwise (The L. E. cell may be found in all three, and also in serum sickness and penicillin reactions). Rather, we should concentrate on this exceedingly important fact: many of these syndromes have so much in common that it seems quite likely that at some undetermined level their mode of production must proceed along common pathways.

If this is true, it may be possible, by trial and error, to find an agent which blocks the pathway in the experimental animal and which might therefore do the same in the spontaneously occurring human disease. Also, a basic study, which the hydralazine-treated experimental animal now permits, may uncover some as yet unsuspected disturbance at an even more fundamental level. In any event, it now seems possible that drug-induced "arthritis," especially the hydralazine syndrome, while creating new clinical problems, may provide a key to the study of the pathogenesis of the various rheumatic diseases.

References

1 Rich, A. R. Hypersensitivity in disease with especial reference to periarteritis nodosa, rheumatic fever, disseminated lupus erythematosus and rheumatoid arthritis. Harvey Lect. *42*: 106-147, 1947.

2 Moser, R. H. Diseases of medical progress. New England J. Med. *255*: 606-614, 1956.

3 Lansbury, J., and Rogers, F. B. The hydralazine syndrome. Bull. Rheum. Dis. *5*: 85-86, 1955.

4 Reinhardt, D. J., and Waldron, J. M.: Lupus erythematosus-like syndrome complicating hydralazine (apresoline) therapy. J.A.M.A. *155*: 1491-1492, 1954.

5 Dustan, H. P., Taylor, R. D., and Page, I. H. Rheumatic and febrile syndrome during prolonged hydralazine treatment. J.A.M.A. *154*: 23-29, 1954.

6 Perry, H. M., Jr., and Schroeder, H. A. Syndrome simulating collagen disease caused by hydralazine (apresoline). J.A.M.A. *154*: 670-673, 1954.

7 Shulman, L. E., and Harvey, A. M. Systemic Lupus Erythematosus. Chicago: Year Book Publishers, May 1956, pp. 10-12.

8 Comens, P. Experimental hydralazine disease and its similarity to disseminated lupus erythematosus. J. Lab. & Clin. Med. *47*: 444-454, 1956.

9 Comens, P. Experimental hydralazine disease. Circulation *12*: 688, 1956.

10 Comens, P. Manganese depletion as an etiological factor in hydralazine disease. Am. J. Med. *20*: 944-945, 1956.

Rehabilitation in Arthritis: the New Concept

by Edward W. Lowman

DESPITE MAJOR ADVANCES of the past decade in the medical therapeutics for arthritis, the place of physical medicine in the basic treatment armamentarium for the prevention of deformity and muscle weakness and for the protection of joints has not diminished in importance Rather, time and experience with newer therapies have re-emphasized even more acutely the value in the prevention of crippling and in the prevention of the need for *rehabilitation of the basic treatment regimen* Details of prophylactic physical medicine programs may be found at length elsewhere.[1] Although they are afforded only cursory consideration here, the inference is not one of disregard but rather an effort to avoid repetition of accepted practices and to focus attention on newer concepts and advances in rheumatologic practice. The problem of the arthritic cripple and the positive progress of the past five years toward development of rehabilitation techniques for its solution represent a dynamic new concept of medical responsibility.[2]

As with all diseases inflicting residual physical disability, the effects of arthritis extend far beyond the limits of the physical While the damage inflicted by the disease is predominantly musculoskeletal, the consequences of the disease ramify into every sphere of the patient's living, reflected not only in incapacity to function physically but in work performance, in psychological adjustment, in stability of the family unit, in recreation, and in every other area of living. Though primarily concerned with the medical aspects of his patient's problem, the physician must consider these ramifications of the disability and direct positive efforts toward solution of them as well as the illness itself if the patient is to be totally benefitted Only thus can he be returned to society to function within the limits of his disability but to the hilt of his capability. In no disease is this expanded concept of medical responsibility more urgent or imperative than in arthritis.

EVALUATION FOR REHABILITATION

In view of the above concept, many types of information are needed in the evaluation of the arthritic before rehabilitation goals may be established (fig. 1). Of first importance is the accurate assessment of the arthritic process both diagnostically and prognostically. In the case of rheumatoid arthritis this is of special importance because the success of physical and vocational rehabilitation to a large extent depends upon the adequacy with

which the progressive disease process may be converted into a stabilized one through the use of antirheumatic medications.

REHABILITATION EVALUATION OF THE ARTHRITIC PATIENT

medical history
physical examination
specialist consultations
laboratory examinations
} DIAGNOSIS AND PHYSICAL PROGNOSIS

muscle test
joint range of motion
speech and hearing evaluation
activities of daily living
} FUNCTIONAL CAPACITY AND POTENTIAL

psychological testing
social survey
vocational testing
} ECONOMIC POTENTIAL

REHABILITATION POTENTIAL

the TOTAL PATIENT must be evaluated

SOCIALLY
PSYCHOLOGICALLY
VOCATIONALLY

as well as

MEDICALLY and
FUNCTIONALLY
before a realistic goal
may be established for the
individual

FIG. 1. The total patient must be evaluated before a realistic goal may be established for the individual

In addition to the medical appraisal, it is equally necessary to evaluate the functional capacity and potentials of the patient in order to project a tentative physical rehabilitation goal. This requires muscle testing to determine the locations and degrees of muscle weakness, measurement of joint ranges of motion to determine the extent and location of joint limitations, and, finally, direct functional testing of the patient in the performance of activities necessary for independent living. Such activities, collectively referred to as "activities of daily living," comprise over a hundred areas of movement, ranging from the simplest bed activities to the most demanding elevation and ambulation activities. Functional testing in activities of daily living is important as corroborative evidence of the patient's ability to

Rehabilitation in Arthritis: the New Con

by Edward W. Lowman

DESPITE MAJOR ADVANCES of the past decade in the medical thera for arthritis, the place of physical medicine in the basic treatment arm tarium for the prevention of deformity and muscle weakness and f protection of joints has not diminished in importance Rather, time experience with newer therapies have re-emphasized even more acutely value in the prevention of crippling and in the prevention of the need rehabilitation of the basic treatment regimen. Details of prophylactic phys medicine programs may be found at length elsewhere[1] Although they a afforded only cursory consideration here, the inference is not one of d regard but rather an effort to avoid repetition of accepted practices and focus attention on newer concepts and advances in rheumatologic practice The problem of the arthritic cripple and the positive progress of the past five years toward development of rehabilitation techniques for its solution represent a dynamic new concept of medical responsibility.[2]

As with all diseases inflicting residual physical disability, the effects of arthritis extend far beyond the limits of the physical While the damage inflicted by the disease is predominantly musculoskeletal, the consequences of the disease ramify into every sphere of the patient's living, reflected not only in incapacity to function physically but in work performance, in psychological adjustment, in stability of the family unit, in recreation, and in every other area of living. Though primarily concerned with the medical aspects of his patient's problem, the physician must consider these ramifications of the disability and direct positive efforts toward solution of them as well as the illness itself if the patient is to be totally benefitted. Only thus can he be returned to society to function within the limits of his disability but to the hilt of his capability. In no disease is this expanded concept of medical responsibility more urgent or imperative than in arthritis

EVALUATION FOR REHABILITATION

In view of the above concept, many types of information are needed in the evaluation of the arthritic before rehabilitation goals may be established (fig. 1). Of first importance is the accurate assessment of the arthritic process both diagnostically and prognostically. In the case of rheumatoid arthritis this is of special importance because the success of physical and vocational rehabilitation to a large extent depends upon the adequacy with



FIG. 5. (top) Motorized wheelchair. (bottom) Adapted feeding utensils.

(7) *Socio-economic and Vocational Factors.* Since the disability of chronic arthritis may ramify its effects permanently into all spheres of living, the need for positive assistance in readjustment to these effects is

(6) *Self-Help Devices.* Irreversible joint deformities which are not amenable to any of the corrective measures mentioned above may mechanically interfere with a patient's performance of function. When these exist, the mechanical problem not infrequently may be bypassed through the use of self-help devices. Furthermore, the performance of a particular activity may impose such traumatic stresses on a joint that as a protection against further wearing of the joint it may be desirable to simplify the activity through the use of an energy-saving device. To be of practical value, a self-help device should be mechanically simple to operate and commercially cheap Great numbers of such pieces of apparatus are now available (figs. 4 and 5), including devices for dressing, for feeding, for personal hygiene, for transportation, for ambulation, and for homemaking.[5]



FIG 4 (upper left) Stocking put on device; (upper right) Spondylitis chair, (lower left) Elevated toilet seat, (lower right) Bathtub rail

It should be pointed out that since rheumatoid arthritis is predominantly a disease of women, and since homemaking is socio-economically important as a vocation, considerable attention recently has been directed toward efficient home-planning and the development of devices for energy conservation by the disabled housewife.[6]

serum, there has been a tendency to assume that the fundamental mechanism in the disease is an immunologic one. This mechanism has usually been allied to the histologically similar diseases that can be produced by hyperimmunization with nonbacterial antigens[5,6] A generation of immunologists and bacteriologists have applied themselves to this problem. McCarty, who has contributed extensively to this field of investigation, has recently pointed out the inconclusiveness of some previously accepted experiments and has highlighted the areas that need review and reinvestigation.[7]

It is accepted that during an epidemic of streptococcal sore throats, the average antibody titers will rise slightly but significantly more in the patients that develop definite rheumatic fever as compared to those who appeared to have escaped rheumatic disease.[8] The rheumatic patients, in retrospect, have also shown initially a higher level of antibodies, suggesting either that they have had more previous streptococcal infections or a greater antibody production than the control population[9] Unfortunately this difference is of no help in predicting susceptibility to rheumatic fever in individual cases, nor in serving as a guide to prophylaxis, because of the very considerable overlap in the data from each group The preceding level of the serum antibodies is also a poor guide to vulnerability amongst younger children in whom the antibody response may be slight, but rheumatic fever itself may be severe A more subtle difficulty in interpreting such antibody studies lies in the limitation of the Jones Criteria[10,11] for the diagnosis of rheumatic fever It seems apparent on clinical grounds that a considerable number of patients suffering from the same biochemical disturbance but in a milder form will be excluded from the "definite" rheumatic fever group and will thus appear in the over all statistics as "those who escaped" Thus, in reality, the antibody titers when averaged, may be correlating with the severity of the pathophysiologic disturbance rather than its presence or absence

A search for manifestations of unusual immunological reactivity in the rheumatic patient other than to streptococcal products has failed consistently to demonstrate abnormalities either as an increased history of other allergic diseases or in qualitative and quantitative abnormalities of specific antibody systems[12,13] Of such studies, the most definitive is that of Kuhns and McCarty[14] in which the secondary response to highly purified diphtheria toxoid was tested in rheumatic and nonrheumatic patients Several parameters of immunologic response were tested, including the development of passive transfer to sensitizing antibodies. No difference from normal was noted in the rheumatic fever patients Thus, at present, no prophylactic regimen based on "desensitization" appears theoretically justified

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Prophylaxis in Rheumatic Fever

by J. E. Warren

A DICUSSION OF PROPHYLACTIC REGIMENS in relation to rheumatic fever may be divided into three categories: (1) prevention of the initial attack of rheumatic fever in apparently normal individuals; (2) prevention of second ary or recurrent attacks in patients who have suffered from rheumatic fever previously; (3) prevention of bacterial endocarditis in patients afflicted with rheumatic valvular heart disease.

Such division of the subject matter does not follow the historical order of development of effective prophylactic programs. Sustained prophylaxis against recurrent attacks of rheumatic fever using sulfanilamide and its derivatives was evaluated adequately by Kuttner and Reyersbach[1] 15 years ago, whereas organized programs against primary attacks of rheumatic fever in the civilian community are just now emerging from the study stage[2,3] A special committee of the Council on Rheumatic Fever and Congenital Heart Disease of the American Heart Association has regularly reviewed the state of knowledge and practice in this field Their recent recommendations will be followed in this presentation.[4]

PREVENTION OF FIRST ATTACKS OF RHEUMATIC FEVER

There is no question at the present time that the development of the clinical syndrome, acute rheumatic fever, is initiated as an unusual reaction of the patient to a preceding infection with a beta-hemolytic streptococcus of Lancefield Group A. Prevention of attacks of rheumatic fever, therefore, should theoretically be directed at modifying the host response or toward minimizing exposure to the precipitating infection. The complete definition and correction of the biologic difference between susceptibility and non-susceptibility to rheumatic attacks would be intellectually more satisfying and probably much more efficient than measures directed against the streptococci However, at the present time the only effective measures to be recommended are antibacterial ones. Widespread application of the antibiotics should markedly reduce the morbidity and mortality from rheumatic fever and rheumatic heart disease in the next generation.

Search for Host Factors

Since the clinically apparent arthritis and carditis of acute rheumatic fever usually appear close to the time when an abrupt increase in circulating antibodies to various streptococcal products is detected in the patient's

serum, there has been a tendency to assume that the fundamental mechanism in the disease is an immunologic one. This mechanism has usually been allied to the histologically similar diseases that can be produced by hyperimmunization with nonbacterial antigens.[5, 6] A generation of immunologists and bacteriologists have applied themselves to this problem. McCarty, who has contributed extensively to this field of investigation, has recently pointed out the inconclusiveness of some previously accepted experiments and has highlighted the areas that need review and reinvestigation.[7]

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the patient is first seen with active rheumatic fever and (b) because of the persistence of the rheumatic disease for many months thereafter, when apparently adequate bactericidal doses of penicillin have been given. However, as pointed out, especially by Eagle[17] and by Denny and Thomas,[18] the streptococcus may survive in an otherwise lethal concentration of penicillin if the organisms remain in a resting state. If rising antibodies or other circumstances should lead to such bacterial hypometabolism during rheumatic fever, these organisms might be capable later of small bursts of activity or slow dissolution with a continued release of antigens into the circulation.

That the mechanism of production of rheumatic fever by streptococci is probably not directly related to the usually measured antibodies is demonstrated by several lines of evidence. Several yearly epidemics of streptococcal pharyngitis was observed by Kuttner and Krumweide[19] in a highly vulnerable rheumatic group of children. The streptococci in one epidemic produced clinical pharyngitis and septic complications, had an "M" substance and produced the expected rise in antistreptolysin 0 titer; yet no recurrence of rheumatic fever occurred, whereas epidemics in the preceding and subsequent years produced the expected number of recurrences More recently, Rammelkamp[20] and his associates have reported that treatment with penicillin as late as the ninth day after onset of pharyngitis still appeared to be capable of preventing subsequent rheumatic fever, although the antistreptolysin 0 responses in these patients were not impressively less than those of the group who received no penicillin nor in those individuals in the "no penicillin group" who subsequently developed rheumatic fever

In our preoccupation with antigen-antibody reactions we have paid too little attention to several other biological potentialities of the streptococci We also have paid too little attention to the possibility that the rheumatic disease is an "overshoot," a "rebound," or hypercompensation to some biochemical stress which occurs during the active streptococcal infection. The streptococcus is a versatile organism [21] It produces an enzyme streptokinase which is a powerful activator of human plasminogen [8, 22, 23] In vivo, activation of this enzyme may alter fibrinogen turnover rates and thus, some of the cardinal disturbances in inflammatory reactions. Investigation of other possible effects upon the clotting mechanism need to be extended in rheumatic disease A resistance to the anticoagulant action of heparin has been noted in acute rheumatic fever[24] but disappears in convalescence, at least it does not persist to a significant degree. The effect of salicylates in producing a decrease in circulating prothrombin and fibrinogen[25] is well known, but whether the metabolism of these substances is abnormal in the rheumatic susceptible patient has not been studied.

Streptolysin "0" has been shown to produce a solubilization of some

lipid protective factor in the mammalian heart.[26] Whether similar effects occur in man and whether an under- or over replacement of the substance occurs during the stage of onset of rheumatic fever has not been investigated. The phenomenon, however, suggests another possible site of a constitutional difference which leads to susceptibility to rheumatic fever. Streptolysin "O" has been shown to combine with free cholesterol[27, 28] and thus lose its lytic properties. The reaction does not occur to any appreciable extent in vitro in normal serum. This observation does not rule out possible interference with cholesterol metabolism in vivo nor with the pathway from cholesterol to the adrenal steroids.

Another fascinating facet of streptococcal biology is the ability of the organism to produce considerable amounts of hyaluronic acid in its capsule.[29] Since this substance is also a "capsular carbohydrate" of the mammalian fibroblast or as we more commonly refer to it "the intercellular cement substance,"[30] it suggests the possibility that the streptococci and the fibroblasts may have similar enzyme systems and thus that the streptococci may also upset its own hyaluronic-acid producing mammalian organism in responding to the infection with hyaluronic acid synthesizing systems. Techniques for investigating hyaluronic acid metabolism in man have not been fully satisfactory. The studies of Bywaters, Holborow and Keech[31] indicated that rheumatic fever patients showed a decreased ability to reform their own hyaluronic acid in the skin after its dissolution by bovine hyaluronidase. Dorfman and others[32, 33] have investigated the pathway of synthesis of hyaluronic acid in group A streptococci but comparable data in man are not available.

Many nutritional, social and environmental studies have been made in relation to rheumatic fever.[34, 35, 36] There seems little doubt rheumatic fever is more frequent in poor, crowded homes. These environmental differences unquestionably increase the risk of streptococcal infections and probably their severity. That dietary inadequacies should change the reaction of the tissues to inflammation seems almost axiomatic in the light of what is known regarding the effects of specific vitamins and protein on tissue and hormonal metabolism. However, whether a specific deficiency of vitamin C or A or protein, etc. is the more important is still subjudice. Nevertheless the provision of a richer diet is quite justified as a prophylactic measure,[36] especially in a family which has experienced one or more cases of rheumatic fever.

Extensive genetic studies have been reported by Wilson[37] and associates. These have been interpreted as showing that the susceptibility to rheumatic fever is inherited as an autosomal recessive gene with incomplete penetrance. Recent communications also stress the role of genetic factors.[38] Unfortunately, because of inadequate family histories and the small size of many families,

genetic data are only occasionally useful in predicting the increased risk of rheumatic attacks in certain families. The variability of the penetrance of the hereditary factor and the all or none nature of a genetic approach to prophylaxis make this an unpromising field for preventive medicine. The presence of a strong family history of rheumatic fever and rheumatic heart disease in the older siblings does justify, in the author's opinion, the use of continuous penicillin prophylaxis throughout at least the school years in the younger members of such a family, although the American Heart Association does not officially make such a radical and pessimistic recommendation.

In recent years, since the advent of hormonal therapy for active rheumatic fever, there have been several attempts to study the spontaneous adrenal corticoid metabolism in the hope that it might reveal a biological difference in the rheumatic patients. While on the staff of the House of the Good Samaritan, Boston, Massachusetts, before the cortisone era, the author attempted to study the hormonal response of known rheumatic patients during and following a recurrent streptococcal pharyngitis. However, the widespread use of penicillin and the impossibility of asking parents to permit omission of penicillin therapy in these children prevented the completion of these studies Such studies might be feasible with adult volunteers, but to date have not been reported

Rheumatic fever is uncommon before the age of 6 years; the highest attack rate is between the ages of 8 and 14.[35, 37] This high incidence is usually attributed to the increased risk of exposure to streptococcal infections in the grade schools, but the attack rate and severity of rheumatic fever following a given streptococcal epidemic is not known for each age group. (In the Army approximately three cases of rheumatic fever developed per 100 streptococcal sore throats) [39]

Streptococcal factors may be paramount but it is worth noting that this appearance of rheumatic fever also parallels the appearance of androgens in the urine. 17-ketosteroids first appear in the urine after age 6 and reach practically adult levels by age 16, with the greatest increase at age 12[44] Since there is evidence that the 17-ketosteroids parallel androgenic activity and that androgens counteract some of the biological effects of corticoids, it is possible that an anomaly of androgen production may occur in the rheumatic patient in response to some specific stimulation of the streptococcal infection. Urinary steroid studies have not revealed biologic differences between the rheumatic patients and suitable controls[45, 46] The inadequacy of urinary steroid assays and the choice of proper controls remain vexing problems. Kelly and his associates have reported the circulating levels of ACTH,[47] of hydrocortisone[48] and corticosterone.[49] Circulating ACTH was elevated and hydrocortisone levels depressed in children who had re-

covered from rheumatic fever. Presumably, therefore, the corticoid response of a child with rheumatic fever may be inadequate. However, the differences between the hydrocortisone levels in the normal and rheumatic group is smaller than the usual wide normal diurnal variations. Hence, it is unwise to depend upon this test to define a group of susceptibles. Furthermore, the time relationships are important. Corticoids, if elevated during a streptococcal infection, might increase the bacterial growth rate and thus, the amount of the biological insult. If, however, corticoids are elevated during the immune reaction and rebound, they might suppress the inflammatory reaction and yet not interfere with prompt over-all recovery. Thus no recommendation for the prophylactic use of hormonal therapy during streptococcal infections is justified on the basis of any published data.

In summary, it may be stated that in spite of the increasing interest in the host factors, a biochemical difference in the response of the rheumatic patient has not been discovered, and there is no effective way of modifying the host response except by eliminating the streptococci.

Attack on the Streptococci

The initial evidence of the effectiveness of antibiotic therapy directed against the streptococcus was developed during follow-up observations of patients who had already recovered from an initial attack of rheumatic fever.[1] However these data have been extensively amplified by the study of streptococcal epidemics and first attacks of rheumatic fever in military populations.[40-43] Sulfadiazine therapy of streptococcal sore throats in the usual doses of 3 to 4 Gm frequently fails to prevent the subsequent appearance of rheumatic fever. This fact was soon recognized in individual cases by physicians caring for rheumatic patients after the introduction and trial of both sulfanilamide and sulfadiazine. Evidence that prompt use of sulfadiazine was also ineffective in preventing first attacks of rheumatic fever has been reported in well controlled studies in the armed services.[50] On the other hand, it has been shown that when penicillin therapy has been administered promptly in streptococcal infections, the expected recurrences of rheumatic activity in a highly vulnerable group of rheumatic patients were prevented. These findings were reported by Massell and associates in 1948 [1] and in 1951.[63] Since the expected attack rate of subsequent rheumatic fever is between 25 and 100 per cent under such circumstances, it was not feasible to be certain of the rheumatogenic potency of the infecting organisms by the use of an extensive alternate case study. Rammelkamp and associates in a series of papers have demonstrated beyond any doubt that penicillin in specifically adequate doses is capable of rapidly eliminating the clinical manifestations of streptococcal pharyngitis and of preventing the subsequent appearance of attacks of rheumatic fever, in a presumably previously normal popula-

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tion.[39, 53] Application of this knowledge to the treatment of all streptococcal infections has recently become a major goal of the American Heart Association.[2, 4] Both individual and mass prophylaxis is now feasible in normal civilian practice.

Mass Prophylaxis During Known Epidemics of Streptococcal Infections

During World War II streptococcal epidemics were a major medical military problem, and the widespread prescription of sulfadiazine in a dose of 1 Gm. per day was demonstrably effective in reducing the carrier rate as well as the number of subsequent cases of clinical pharyngitis and the attack rate for rheumatic fever.[40] However, because of the emergence of sulfa-resistant organisms[54] and the risk of toxic reactions as well as the ineffectiveness of this dosage in established infections, it has been largely superseded by the use of oral penicillin. For such mass prophylaxis during epidemics, oral medication is the only satisfactory form.[55] Present problems center around the minimally effective dose and the form of the penicillin used. Poskanzer, Feldman and Beadenkopf[3] have recently reported the study of two epidemics in comparable school populations of approximately 500 each. In each school, throat cultures were taken on about 25 per cent of the pupils and a uniform dose of oral penicillin G was given for 10 days to almost the entire school. The results in terms of elimination of positive cultures are as follows:

TABLE 1

RESULTS OF PENICILLIN MASS PROPHYLAXIS IN TWO SCHOOL EPIDEMICS

School	Dosage	PER CENT POSITIVE THROAT CULTURES				
		Before Rx	*7-10 Days*	*21 Days*	*55-62 Days*	*Over-all Effect*
A	250,000 U twice daily	31	0	5	10	Epidemic subsided
B	250,000 U once daily	38	20	32	38	Epidemic persisted

It is noteworthy that in school A there was almost complete elimination of the carrier state; the few recurrent carriers may perfectly well have been reinfections from the small foci of infection still in the community. However, clinically, the epidemic subsided and the absentee rate in the school soon dropped to the normal base line. In school B, in which only one tablet per day was used, almost half the carrier rate continued and rapidly returned to the initial level after omission of the therapy. The epidemic persisted to such an extent that it was eventually necessary to close the school two months after the epidemic had started. The small decrease in the carrier

state as noted in the second group is hardly greater than the spontaneous disappearance of positive cultures that has been noted in military experience.[56] Thus, a lower limit for the dosage of penicillin to be used in eliminating clinically apparent or inapparent infection must be equivalent to the schedule used in school A. One should remember when considering these data that although the word prophylaxis is used, it is the prophylaxis of subsequent rheumatic fever in which we are primarily interested. These data of Poskanzer, Feldman and Beadenkopf measure the effectiveness of penicillin in eliminating known infections during an epidemic with a virulent organism. Massell's data[33] also showed that dosage of 100,000 units t.i.d. in clinically well carriers was sometimes ineffective in eliminating the carrier state, although this dosage may be adequate to prevent new infections. Since the bactericidal effect of penicillin depends upon the concentration of active organisms and their rate of metabolism, as well as upon the concentration of the antibiotic at any given locus,[17, 15] it probably is rather slowly effective in the crypts of the tonsils where bacterial mass may be high and metabolism low. Since the patient has had little opportunity to form protective antibodies, a recrudescence of the infection is possible if antibiotic therapy is not maintained for a period of ten days.

The author still prefers oral penicillin because of the lesser incidence and duration of allergic reactions, but since patient cooperation in continuing the program for 10 days is often in doubt, many physicians now favor the use of intramuscular benzathine penicillin for sustained therapeutic effect.[57, 58] Erythromycin has equal bactericidal potency in such circumstances and can be used as a substitute in those patients who report penicillin sensitivity.[4] Chlortetracycline therapy also appeared effective in preventing rheumatic recurrences when used in a military setting, however, throat cultures frequently remained positive, the patient's associates were exposed to similar infections, and an epidemic could thus be perpetuated.

Individual Cases of Streptococcal Pharyngitis In Normal Medical Practice

The major medical problem is in differentiating streptococcal from other types of pharyngitis. The common differential diagnostic points may be summarized as follows:[4]

COMMON SYMPTOMS

Sore throat	sudden onset, pain on swallowing
Headache	common
Fever	variable, but generally from 101° to 104° F.
Abdominal pain	common, especially in children
Nausea and vomiting	common, especially in children

COMMON SIGNS
- *Red throat* — usually present
- *Exudate* — usually present
- *Glands* — swollen, tender lymph nodes at angle of jaw
- *Rash* — scarlatiniform
- *Acute otitis media* — frequently due to the
- *Acute sinusitis* — streptococcus

LABORATORY FINDINGS
- *Throat culture* — hemolytic streptococci (almost invariably recovered on culture during acute phase)
- *White blood Count* — generally over 12,000/mm.

In the absence of the common symptoms and signs, occurrence of any of the following symptoms is usually not associated with a streptococcal infection: simple coryza, hoarseness and cough.

The differential diagnosis is often difficult and is especially so in younger children. An appeal is made for the more extensive use of throat cultures at the time of the first examination The recommended technique for detecting positive cultures is outlined in a readily available reprint from the American Heart Association,[4] essentially, it consists of the prompt swabbing of tonsillar and pharyngeal areas and streaking this material upon a sheep red cell agar plate. After 24 hours of incubation, the colonies of beta hemolytic streptococci are readily identifiable The practical problem is to increase the availability and ease with which the cultures can be incubated and positive cultures reported promptly to the physician An increase in the availability of local incubators in health department substations and the daily collection of the incubating cultures for examination by a central laboratory seems to be an excellent program for sponsorship by the local heart associations and public health authorities. The 24 or 48 hour delay in therapy before obtaining a cultural report does not seem to decrease the effectiveness of penicillin therapy in the prophylaxis of rheumatic fever.[20] However, this may not hold true for the more violent infections in relation to the prevention of post-streptococcal glomerulonephritis.[59] Further discussion of the problem of both the diagnosis of streptoccocal infections and the choice of effective therapy, especially in individual cases in children, have been reported by Breese and Disney.[60, 61]

Sensitivity reactions to oral penicillin in adults have been reported to be of the order of .3 to .7 per cent when given over a period of several months. Control studies with placebos in the same circumstances have revealed reactions of the order of 2 per cent at a time when penicillin reactions were reported as .3 per cent[55] These reactions were usually of the nature

of mild generalized urticaria. Since this suggests that perhaps half or more of suspected reactions may not be due to the penicillin itself, one is thoroughly justified in restarting oral penicillin after a few days as a further trial of the presence or absence of sensitivity. Anaphylactoid reactions to oral penicillin should preclude further use of this medication.[52] Sensitivity to parenteral benzathine penicillin is of a different order of magnitude and has been reported between 1 and 5 per cent depending upon whether 0.6 or 1.2 million units were injected. Also, there is a tendency for the sensitivity to be much more prolonged under these circumstances.[52]

Finally, we cannot close the discussion of the effectiveness of penicillin therapy of streptococcal infections in preventing initial attacks of rheumatic fever without a discussion of the dissenting opinions reported by Weinstein and his group on the basis of their observations in patients with scarlet fever. They have concluded that the incidence of subsequent rheumatic fever may be unchanged but that the severity of the disease has been markedly diminished by penicillin therapy of the preceding scarlet fever.[54] The initial report was based largely upon the frequency with which abnormal ECG changes were noted during convalescence from scarlet fever despite penicillin therapy. In a more recent follow-up they have reported that a surprising number of the originally subclinical cases have now developed murmurs of valvular heart disease without intervening clinical episodes of rheumatic fever.[55] Comparable studies carried out by Levander-Lindren[56] included a small group of controls who were not given penicillin. When those who received penicillin and those who did not were compared, the treated group had approximately 3 per cent abnormalities in the ECG whereas 5 per cent of the controls showed comparable changes. Nevertheless, only 1 out of 110 patients with ECG abnormalities showed auscultatory evidence of valvular heart disease when examined from one to five years later. In another study by Stolzer, Houser and Clark,[57] approximately 50 per cent of the 138 adult male patients who had daily ECG's showed abnormalities of AV conduction during the course of rheumatic fever, and yet 60 per cent of them showed no heart disease when examined 14 months later. Mortimer and Rammelkamp[58] have presented an extensive critique of this problem and conclude that there is no doubt that adequate treatment of the preceding streptococcal infection reduces the incidence of clinical rheumatic fever as well as reducing considerably the ECG abnormalities which are so common following streptococcal infections. They also suggest that there is no close correlation between the amount of electrocardiographic abnormalities noted after streptococcal infections and the development of subsequent clinically recognizable rheumatic endocardial changes. Whether the present use of antibiotic therapy will markedly reduce the incidence of late or delayed appearance of mitral stenosis, will require perhaps another five years of follow-up studies. The

evidence, however, is sufficiently strong so that we should continue to urge the widespread and prompt use of penicillin in all streptococcal infections.

The foregoing discussion is primarily directed at the treatment of streptococcal infections in persons not previously diagnosed as having suffered from rheumatic fever. However, if while examining a patient with an acute respiratory infection a history of previous rheumatic fever is obtained or definite rheumatic heart disease is recognized and yet this patient is somehow or other not on regular continuous prophylaxis, then the diagnostic and therapeutic approach is essentially the same as outlined. Throat cultures and serum for antistreptolysin O tests should be drawn routinely in such cases in order to facilitate the differential diagnosis if persistent or recurrent febrile episodes occur in the next few weeks and the problem of a possible recurrence of rheumatic fever be raised. In addition, if the patient has been on sulfadiazine prophylaxis, white counts and differential counts are indicated because agranulocytosis may be the fundamental cause of the development of the pharyngitis. Also, differential smears may reveal mononucleosis, and since ECG abnormalities have been described in this disease, a further simulation of rheumatic carditis following a pharyngitis ca: occur.[68]

The present recommendations of the American Heart Association are as follows.

TREATMENT OF KNOWN OR SUSPECTED STREPTOCOCCAL PHARYNGITIS

Intramuscular Benzathine Penicillin G

Children—one intramuscular injection of 600,000 to 900,000 units

Adults —one intramuscular injection of 900,000 to 1,200,000 units

or

Intramuscular Procaine Penicillin with Aluminum Monostearate in Oil

Children—one injection of 300,000 units every third day for three doses

Adults —one injection of 600,000 units every third day for three doses

Oral Penicillin G or V

Children—600,000-750,000 units per day in three divided doses for full 10 days

Adults —600,000-750,000 units per day in three divided doses for full 10 days.

The usual oral preparation until now has been buffered penicillin G; however, comparative studies of the new oral penicillin V in children have indicated an equally rapid absorption and a more sustained concentration when identical dosages are used.[69] If the cost of G and V are eventually equalized the latter compound will probably be preferred. The same authors have also observed that higher blood levels were obtained when the medica-

tion was given 30 minutes after meals than when given as is usually done on an empty stomach. Presumably, therefore, either the rate of destruction in the gastrointestinal tract is less or absorption greater when given at the time of meals. This is of considerable practical value since it means that the critical morning dose of medicine need not be given prior to breakfast and yet effective levels can be maintained throughout the usual school hours. It would also seem preferable to administer the second dose in mid-afternoon so that any organisms that have been acquired during the day can be eliminated before they have a chance to multiply.

PREVENTION OF SECONDARY OR RECURRENT ATTACKS OF RHEUMATIC FEVER

Much of the discussion in the previous presentation is also pertinent in this section. Therapy for the prevention of secondary attacks of rheumatic fever should begin at the time a diagnosis is first suspected during the active disease in the first rheumatic attack. Throat cultures should first be taken, followed by penicillin given essentially in full dosage for ten days as previously outlined for suspected streptococcal pharyngitis. Continuous administration is indicated thereafter to prevent the same or other streptococci from reimplantation. The risk of superinfection with another strain of streptococci may be greater in a hospital than at home, but a major diagnostic problem may develop in such surroundings since antirheumatic therapy, e.g., salicylates, may mask the pharyngeal discomfort and fever which are the main clinical indications of a recent streptococcal pharyngitis, yet the vulnerability to exacerbation of rheumatic fever in such a patient is extremely high. This problem is intimately related to the management of acute rheumatic fever and is discussed in detail in the section by Stollerman.

When rheumatic fever has become quiescent, continuous prophylaxis must be thoroughly "sold" to parents and patients. The initial observations of the effectiveness of sulfanilamide in doses of 0.5 to 1.0 gram per day have been amply confirmed using sulfadiazine.[70, 71] There remains the necessity for laboratory control of the leukocyte count and urinary findings, especially during the first two months of such a regimen. However, the emergence of sulfa resistant strains of beta-hemolytic streptococci has not been critical despite a widespread problem of sulfadiazine resistance in army experience in World War II.

Most recent experience has been with penicillin prophylaxis.[72] Oral penicillin in doses of 100,000 units to 300,000 units per day has been extensively used and has been effective in preventing streptococcal sore throat, under most circumstances. However, recent reports that 250,000 units per day was ineffective[73] in preventing the spread of an epidemic in a hospital for rheumatic fever patients has led to an upward revision of the recommended

dosage in known rheumatic patients.[4] Frequently in clinic practice, as well as in private practice, apathy develops in parents or patients so that oral medication is not continuous When this occurs and a streptococcal pharyngitis appears, subsequent return to the usual prophylactic dosage may be inadequate for rapid eradication of the streptococci and recurrences of rheumatic fever may be expected. The difficulty in maintaining continuous prophylaxis with oral medication which is dependent upon patient cooperation has recently led to a widespread preference for the use of benzathine penicillin intramuscularly at monthly intervals.[74] Fortunately, the beta-hemolytic streptococcus is highly sensitive to penicillin and effective bactericidal levels can be maintained throughout the month. Benzathine penicillin is painful at the site of injection for several days and fever and objective evidence of inflammation is not uncommon.[62] Sensitivity reactions, if they occur, can be exasperatingly prolonged. Because of these objections, the author prefers to continue with oral penicillin with 100,000 units t.i d or 250,000 units b.i d. if there is reasonable assurance that patient and parent will cooperate. Reactions to oral penicillin are less frequent but can be equally severe [63]

The practicability of preventing recurrent attacks of rheumatic fever by continuous prophylaxis has now been demonstrated so conclusively that the most critical current problem is the determination of who should be on continuous prophylaxis followed by the establishment of the administrative machinery for the follow-up in the office or clinic and the provision for intense and effective education.[75] Since rheumatic recurrences can occur at any age or interval after the previous attack, and since a streptococcal infection can occur at any season, penicillin prophylaxis is "for life" Admittedly the vulnerability to recurrent streptococcal infection and to subsequ rheumatic fever may be less during adult life than in the school years. Ho ever, the sociological damage produced by a recurrence of rheumatic fev in a 30-year-old mother or father of several children can be so enormou the conscientious physician will not permit a relaxation of the prophylacti regimen. Some adults will not be convinced. Under such circumstances, the must be urged to receive penicillin therapy promptly for suspected streptococcal pharyngitis.

Once the diagnosis of rheumatic fever has definitely been established according to the Jones Criteria, the only choice remaining is the form of prophylactic therapy. However, any practicing physician is aware of the frequency with which one sees less definite syndromes While the Criteria of Jones have attained worldwide acceptance as a description of the disease suitable for statistical control in studies of the natural history or therapeutic trials, it has always been recognized by those working in the field that the biological fault probably occurred at least as frequently in an even milder

form This milder form may carry statistically a lesser risk of recurrence but not necessarily so In clinical practice, this indefinite group has been covered usually by the diagnosis of "probable" or "possible" rheumatic fever when a combination of indefinite arthralgia, prolonged lassitude and anemia occurred during the convalescent stage of a streptococcal infection, and a more definite diagnosis is not justified. Whether one recommends penicillin prophylaxis during the school years for such a patient is primarily dependent upon one's own philosophy. In practice, I have recommended continuous oral penicillin in such circumstances when the patient seemed intelligent and unlikely to develop cardiac neurosis and the economic factor was not a hindrance. Since I have observed violent rheumatic fever subsequent to streptococcal infections in such cases more often than I have seen psychological damage from continuous prophylaxis, I am perhaps more radical than others. Most physicians consider it preferable to withhold continuous prophylaxis when the diagnosis is uncertain

The present recommendations of the American Heart Association are given below. Three major choices of therapy are approved

PREVENTION OF STREPTOCOCCAL PHARYNGITIS IN KNOWN RHEUMATIC PATIENTS

(1) *Benzathine penicillin G—Intramuscular*

Dosage: 1,200,000 units once a month

Notes: Toxic reactions are the same as with oral penicillin but occur more frequently and tend to be more severe Some local discomfort is usually experienced

(2) *Sulfadiazine—Oral Tablets*

Dosage 1 0 gram per day (0 5 Gm. for children under 60 lbs.)

Notes Easy to administer, inexpensive and effective. Toxicity infrequent and usually minor. All rashes and sore throats may be toxic reactions Check WBC and differential weekly for first eight weeks. Change therapy if WBC is less than 4,000 or PMN are less than 35%.

Morbilliform rash continue drug with caution.

Urticaria or scarlatiniform eruption with pharyngitis, omit drug

(3) *Penicillin—Oral tablets*

Dosage: 200,000 to 250,000 units once or twice per day

Twice a day preferable

Notes Highly bactericidal for Group A streptococci Rarely toxic. Carefully check history for allergic reactions, e g., urticaria

dosage in known rheumatic patients[4] Frequently in clinic practice, as well as in private practice, apathy develops in parents or patients so that oral medication is not continuous. When this occurs and a streptococcal pharyngitis appears, subsequent return to the usual prophylactic dosage may be inadequate for rapid eradication of the streptococci and recurrences of rheumatic fever may be expected. The difficulty in maintaining continuous prophylaxis with oral medication which is dependent upon patient cooperation has recently led to a widespread preference for the use of benzathine penicillin intramuscularly at monthly intervals.[74] Fortunately, the beta hemolytic streptococcus is highly sensitive to penicillin and effective bactericidal levels can be maintained throughout the month. Benzathine penicillin is painful at the site of injection for several days and fever and objective evidence of inflammation is not uncommon.[62] Sensitivity reactions, if they occur, can be exasperatingly prolonged. Because of these objections, the author prefers to continue with oral penicillin with 100,000 units t.i.d or 250,000 units b.i.d. if there is reasonable assurance that patient and parent will cooperate. Reactions to oral penicillin are less frequent but can be equally severe[63]

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and better still that an injection of 600,000 of aqueous and 600,000 units of procaine penicillin be given before the procedure.[4] When operations are contemplated upon the intestinal or urinary system, there is a greater likelihood of enterococcal bacteremia. Under such circumstances, resistance to penicillin is considerably greater than with the salivary organisms, and streptomycin or one of tetracyclines should be added to the program in full dosage for five days as outlined above In most patients with penicillin sensitivity, erythromycin promises to be an effective substitute

Fortunately, there appears to be an appreciable gap between the dose of penicillin sufficient to prevent beta-hemolytic streptococcal infection (i e., less than .04 units per ml) and the amount which is usually required to suppress the viridans group (i.e , greater than 0.1 unit per ml). Thus, there has been no marked tendency for resistant strains of green streptococci to appear in the rheumatic patients on regular long-term prophylaxis However, the extensive use of penicillin in higher doses in surgical infections may favor survival of the more resistant enterococci There are no control studies available of the effectiveness of these regimens for the prevention of subacute bacterial endocarditis, but the recurring appearance of patients with subacute bacterial endocarditis who give a definite history of dental extractions or prior surgery and who have not had prophylaxis is to be regretted The isolation from these patients of organisms which respond quite adequately to the dosage of medications outlined here thoroughly justifies the insistence upon the application of this program in all patients with rheumatic endocarditis. It is worth noting that in many of the patients who have dental extractions there may well have been sufficient dental sepsis to have introduced organisms into the blood stream before any dental manipulation was carried out, so that the presence of dental sepsis itself suggests use of additional antibiotics in patients with rheumatic and other types of endocardial heart damage

PROPHYLAXIS AGAINST BACTERIAL ENDOCARDITIS

First Choice	*Oral Plus Intramuscular*
Day 1 and 2	200,000 250,000 units oral penicillin four times a day
Day 3 (operation)	200,000-250,000 units oral penicillin four times a day (600,000 units aqueous penicillin, 600,000 units procaine penicillin shortly before surgery)
Day 4 and 5	200,000-250,000 units oral penicillin four times a day

Second choice is to administer the identical five-day oral penicillin dosage but omit the added certainty provided by the intramuscular injections

angioneurotic edema. Serum sickness with fever and joint pains may suggest rheumatic fever. Many individuals with mild skin erythematous reactions or an episode of hives while on penicillin have subsequently taken the drug with no further reactions. However, this practice is not recommended if the reaction has been severe or angioneurotic edema has occurred.

Prophylaxis Against Bacterial Endocarditis

As we have progressed in our apparent ability to prevent recurrent attacks of rheumatic fever and the subsequent rheumatic heart disease, a concurrent battle has been waged against one of the major complications of already established rheumatic heart disease, namely, bacterial endocarditis.[76] Therapy of this once invariably fatal disease has been markedly improved since the advent of penicillin and enhanced with the addition of other antibiotics. However, the disease still carries a 10-20 per cent mortality and a marked morbidity due to cerebral, renal and other types of cardiovascular damage. Prevention of the disease is much less effective than the programs for prevention of rheumatic fever since the source of precipitating infections is unknown in at least one-half the cases. However, a sufficient proportion (30-40 per cent) give a history of a preceding dental or surgical operation in an area of sepsis so that prophylactic measures are aimed at minimizing these known risks.

The presence of bacteremia with organisms of the streptococcus viridans group has been repeatedly demonstrated after manipulative procedures or extraction of teeth.[77] Clinically, a history of preceding dental extractions is the commonest single suspicious event in histories of patients afflicted with subacute bacterial endocarditis, although it may account for not more than 20 per cent of the total cases. Since the organisms recovered in the blood cultures after dental extractions are those predominantly found as the cause of bacterial endocarditis, the clinical impression of the role of dental sepsis seems well established. However, many operative procedures, especially those involving the lower gastrointestinal, genitourinary, or pelvic organs or criminal abortions, have also been noted in the histories of these patients.

The usual organism found as a cause of bacterial endocarditis is the alpha "green" hemolytic streptococcus. Since these organisms are less sensitive to penicillin than are the beta-hemolytic streptococci, considerably higher dosages are required for prophylaxis, although for only a few days. The minimal recommended dose is at least twice as high as in the usual long-term prophylactic regimen It should be given for a total of five days starting two days before the extraction or surgery and continuing for two days thereafter. Since a high bactericidal dose is desired immediately after surgery, it is recommended that the daily dose be again doubled prior to surgery

serum antistreptolysin and gamma globulin levels, with special reference to occurrence of rheumatic fever J Clin Invest 27 425, 1948

9 McCarty, M · The immune response in rheumatic fever In Rheumatic Fever, L. Thomas Minneapolis, Univ of Minnesota Press, 1952

10 Jones, T D The diagnosis of rheumatic fever J A M A 126 481, 1944

11 American Heart Association report of the committee on standards and criteria for programs of care of the Council on Rheumatic Fever Jones Criteria (modified) for guidance in the diagnosis of rheumatic fever Mod Concepts Card Dis 24 291, 1955

12 Miller, J M., Kibrick, S., and Massell, B F Antibody response to non streptococcal antigens as related to rheumatic fever susceptibility J Clin Invest 32 691, 1953

13 Creger, W P., Choy, S H., and Rantz, L A Experimental determination of the hypersensitive diathesis in man J Immunol 66: 445, 1951

14 Wagner, V and Rejholec, V Agglutinins and incomplete antibodies after a single antigenic inoculation in normal and rheumatic individuals Ann Rheum Dis 14 243, 1955

15 Quinn, R W., Seastone, C V., and Dickie, H A Antibody production and tuberculin sensitivity in individuals with a history of rheumatic fever J Immunol 70 493, 1953

16 Kuhns, W. J., and McCarty, M · Studies of diphtheria antitoxin in rheumatic fever subjects analysis of reactions to the Schick test and of antitoxin responses following hyperimmunization with diphtheria toxoid J Clin Invest. 33 759, 1954

17 Eagle, H., Fleishman, R., and Musselman, A D Effect of schedule of administration on the therapeutic efficiency of penicillin Am J Med 9 280, 1950

18 Denny, F W., Jr., and Thomas, L. Persistence of group A streptococci in tissues of rabbits after infection Proc Soc Exper Biol & Med 88 260, 1955

19 Kuttner, A G., and Krumwiede, E Observations on the effect of streptococcal upper respiratory infections on rheumatic children 3 year study J Clin Invest 20 273, 1941

20 Catanzaro, F J., Stetson, C A., Morris, A J., Chamovitz, R., Rammelkamp, C H., Jr., Stolzer, B L., and Perry, W D The role of the streptococcus in the pathogenesis of rheumatic fever Am J Med 17 749, 1954

21 McCarty, M The biology of group A hemolytic streptococci in rheumatic fever symposium, ed. L Thomas Minneapolis, Univ of Minnesota Press, 1952

22 Kaplan, M H Nature and role of the lytic factor in hemolytic streptococcal fibrinolysis Proc Soc Exp Biol & Med 57 40, 1944

23 Christensen, L R The streptokinase-plasminogen system In Streptococcal Infections, ed M McCarty New York, Columbia Univ Press, 1954

24 Abrahams, G D and Glynn, L E Heparin tolerance in rheumatic fever Clin Science 8 171, 1949

25 Gross, M and Greenberg, L. The Salicylates, a Critical Bibliographic Review New Haven, Hillhouse Press, 1948

26. Bernheimer, A W., and Cantoni, G L The cardiotoxic action of preparations containing the oxygen labile hemolysin of streptococcus pyogenes III J Exp Med 86 193, 1947

27 Hewitt, L F., and Todd, E W The effect of cholesterol and of sera contaminated with bacteria on hemolysins of hemolytic streptococci J Path Bact 49 45, 1939

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SUMMARY

Prophylactic regimens in the several aspects of rheumatic fever have now become sufficiently effective so that there is no excuse for their omission Our problems have resolved themselves into the provision for widespread dissemination of knowledge and enforcement of the recommendations It is at this level that community education and community support should be most effective. With the widespread application of such a program, we can anticipate a considerable reduction in the severity and almost certainly in the incidence of rheumatic heart disease in the coming generation. This is a timely advance, for it is not generally appreciated that the number of children in the highly vulnerable age group of 8 to 14 years in the United States has nearly doubled in the past 10 years. If prophylaxis had not become available, we might very well have been overwhelmed with streptococcal infections and rheumatic fever because of the crowded conditions of many of our schools

References

1 Kuttner, A G., and Reyersbach, G. The prevention of streptococcal upper respiratory infections and rheumatic recurrences in rheumatic children by the prophylactic uses of sulfanilamide. J. Clin Invest *22:* 77, 1943
2 Hubbard, J P Prevention of first attack rheumatic fever Ann Int Med *43* 504, 1955
3 Poskanzer, D C, Feldman, H A, and Beadenkopf, W G · Mass penicillin prophylaxis in the control of civilian streptococcal epidemics. Ann Rheum Dis *15*· 389, 1956
4 American Heart Association report of the committee on prevention of rheumatic fever and bacterial endocarditis. Prevention of rheumatic fever and bacterial endocarditis through control of streptococcal infections Mod. Concepts Card Dis *25* No 12 (Suppl), 1956
5 Rich A R. Hypersensitivity in disease with special reference to periarteritis *nodosa, rheumatic fever, disseminated lupus erythematosus and* rheumatoid arthritis Harvey Lect *42*, 106, 1947.
6 Murphy, G E, and Swift, H F Induction of cardiac lesions, closely resembling those of rheumatic fever, in rabbits following repeated skin infections with group A streptococci J Exper Med *89* 687, 1949
7. McCarty, M Nature of rheumatic fever Circulation *14* 1138, 1956
8. Anderson, H. C. Kunkel, H G, and McCarty, M · Quantitative antistreptokinase studies in patients infected with group A hemolytic streptococci, a comparison with

serum antistreptolysin and gamma globulin levels, with special reference to the occurrence of rheumatic fever J Clin. Invest. 27 425, 1948
9 McCarty, M The immune response in rheumatic fever *In*. Rheumatic Fever, ed L. Thomas Minneapolis, Univ of Minnesota Press, 1952
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12. Miller, J M, Kibrick, S, and Massell, B F - Antibody response to non streptococcal antigens as related to rheumatic fever susceptibility J Clin Invest *32* 691, 1953
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17 Eagle, H., Fleishman, R, and Musselman, A D.. Effect of schedule of administration on the therapeutic efficiency of penicillin Am J Med. *9* 280, 1950
18 Denny, F W., Jr, and Thomas, L. Persistence of group A streptococci in tissues of rabbits after infection Proc. Soc Exper Biol & Med *88* 260, 1955
19 Kuttner, A. G, and Krumweide, E Observations on the effect of streptococcal upper respiratory infections on rheumatic children 3 year study J Clin Invest. *20* 273, 1941
20 Catanzaro, F J, Stetson, C A, Morris, A J, Chamovitz, R, Rammelkamp, C H, Jr, Stolzer, B L., and Perry, W D The role of the streptococcus in the pathogenesis of rheumatic fever Am J Med *17* 749, 1954
21 McCarty, M The biology of group A hemolytic streptococci in rheumatic fever symposium, ed L Thomas Minneapolis, Univ of Minnesota Press, 1952
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24 Abrahams, G D and Glynn, L. E Heparin tolerance in rheumatic fever Clin Science *8* 171, 1949
25 Gross, M and Greenberg, L The Salicylates, a Critical Bibliographic Review New Haven, Hillhouse Press, 1948.
26 Bernheimer, A W, and Cantoni, G L. The cardiotoxic action of preparations containing the oxygen labile hemolysin of streptococcus pyogenes. III J. Exp Med *86* 193, 1947
27 Hewitt, L. F, and Todd, E W. The effect of cholesterol and of sera contaminated with bacteria on hemolysins of hemolytic streptococci J Path Bact *49* 45, 1939
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References

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2. Hubbard, J. P.: Prevention of first attack rheumatic fever. Ann. Int. Med. *43*: 504, 1955.
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5. Rich, A. R.: Hypersensitivity in disease with special reference to periarteritis nodosa, rheumatic fever, disseminated lupus erythematosus and rheumatoid arthritis. Harvey Lect. *42*: 106, 1947.
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3. Poskanzer, D. C., Feldman, H. A., and Beadenkopf, W. G.: Mass penicillin prophylaxis in the control of civilian streptococcal epidemics. Ann. Rheum. Dis. 15, 389, 1956.
4. American Heart Association report of the committee on prevention of rheumatic fever and bacterial endocarditis: Prevention of rheumatic fever and bacterial endocarditis through control of streptococcal infections. Mod. Concepts Card. Dis. 25, No. 12 (Suppl.), 1956.
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52 Massell, B F, Sturgis, G P, Knoblock, J D, Streeper, R B, Hall, T. N, and Norcross, P Prevention of rheumatic fever by prompt penicillin therapy of hemolytic streptococcic respiratory infections. J A M A 146 1469, 1951

53 Denny, F W, Wannamaker, L. W, Brink, W R, Rammelkamp, C H, Jr, and Custer, E. A Prevention of rheumatic fever Treatment of the preceding streptococcal infection J A M A 143 151, 1950.

54 Johnson, R D, and Hartman, T L Sulfadiazine resistant streptococcal infections in civilian community J Clin Invest 26. 325, 1947

55 Bernstein, S H, Feldman, H A, Harper, O F, Jr, Klingensmith, W. H, and Cantor, J A Observations in Air Force recruits of streptococcal disease and their control with orally administered penicillin J Lab & Clin Med 44 1-13, 1954

56 Houser, H B, Eckhardt, G C, Hahn, E O, Denny, F W, Wannamaker, L W, and Rammelkamp, C H, Jr Effect of Aureomycin treatment of streptococcal sore throat on the streptococcal carrier state, the immunologic response of the host and the incidence of acute rheumatic fever Pediatrics 12 593, 1953

57 Chamovitz, R, Catanzaro, F J, Stetson, C A, and Rammelkamp, C H Jr Prevention of rheumatic fever by treatment of previous streptococcal infection evaluation of benzathine penicillin G New England J Med 251 466, 1954

58 Brooks, T J, and Moe, T I Use of benzathine penicillin G in carriers of group A beta hemolytic streptococci. J A M A 160 162, 1956

59 Rammelkamp, C H, Jr Present status of streptococcal infections in relation to rheumatic fever and glomerulonephritis, Am J Clin Path 26 555, 1956

60 Breese, B B Treatment of beta hemolytic streptococcic infections in the home Relative value of available methods J A M A 152 10, 1953

61 Breese, B B, and Disney, F A The accuracy of diagnosis of beta streptococcal infections on clinical grounds J Pediat 44 670, 1954

62 Haas, R C, Taranta, Angelo, and Wood, H F Effect of intramuscular injections of benzathine penicillin G on some acute phase reactants New England J Med 256 152, 1957

63 Maganzini, H C Anaphylactoid reaction to penicillins V and G administered orally Report of two cases and brief review of the subject. New England J Med 256 52, 1957

64 Weinstein, L, Bachrach, L, and Boyer, N H Observations on the development of rheumatic fever and glomerulonephritis in cases of scarlet fever treated with penicillin New England J Med 242 1002, 1950

65 Weinstein, L, Boyer, N H, and Goldfield, M Rheumatic fever in scarlet fever patients treated with penicillin A follow-up study after seven years New England J Med 253 1 1955

66 Levander Lindgren M Electrocardiographic studies in scarlet fever Acta Paediat, Suppl 91 1952

67 Stolzer, B L, Houser, H B, and Clark, E J Therapeutic agents in rheumatic carditis Comparative effects of acetylsalicylic acid, corticotropin and cortisone Arch Int Med 95 677, 1955

68 Warren, J E Unpublished observations.

69 Holborow, E. J, Bywaters, E. G L, and Johnson, G D Blood levels after penicillin G or V in children Brit. M J 2 1338, 1956

70 Bundy, W E, McCue, C M, and Porter, R R The control of rheumatic f recurrences with sulfadiazine and gantrisin J Pediat 41 320, 1952

71 Kuttner, A G Prevention of rheumatic fever and rheumatic heart disease Pc Grad Med 14 429, 1953

charide elaborated by mucoid strains of group A hemolytic streptococcus J Biol Chem *118* 61, 1937

30 Meyer, K. The biological significance of hyaluronic acid and hyaluronidase Phys. Rev *27*. 335, 1947

31 Bywaters, E. G L, Holborow, E. J., and Keech, M K.: *Reconstitution of the dermal* barrier to dye spread after hyaluronidase injection. Brit. M. J *2*. (Nov) 1951

32 Roseman, S, Moses, F. E., Ludowieg, J., and Dorfman, A. The biosynthesis of hyaluronic acid by group A streptococcus; utilization of I-C[14] glucose J Biol Chem *203*: (July) 1953

33 Dorfman, A., and Cifonelli, J. A: Biosynthesis of hyaluronic acid by group A streptococci Ann Rheumatic Dis. *15*· 378, 1956

34 Paul, J R. Epidemiology of rheumatic fever. Am J. Med. *2*· 66. 1947

35 Thomas, L. (editor): Rheumatic Fever, a Symposium Minneapolis, Univ of Minn Press, 1952.

36 Coburn, A F. *Problems in the prevention of rheumatic fever by a reinforced diet.* J Am Dietetic Assoc *26*: 345, 1950.

37 Wilson, M. G. Rheumatic fever The Commonwealth Fund. New York, Oxford Univ Press, 1940

38 Eleventh Rheumatism Review Ann Int Med *45* 859, 1956

39 Mortimer, E A., Jr, and Rammelkamp, C. H., Jr· Prophylaxis of rheumatic fever Circulation *14* 1144, 1956

40 *Coburn, A F, and Young, D C. The Epidemiology of Hemolytic Streptococcus* During World War II in the U. S Baltimore, Williams & Wilkins, 1949

41 Catanzaro, F J, Brock, L, Chamovitz, R, Perry, W D, Siegel, A. C, Stetson, C A., Rammelkamp, C. H, Jr., Houser, H B, Stolzer, B L., Wannamaker, L. W., and Hahn, E. O: Effect of oxytetracycline therapy of streptococcal sore throat on the incidence of acute rheumatic fever Ann Int. Med *42*, 345, 1955

42 Wannamaker, L. W.· The epidemiology of streptococcal infections *In*· Streptococcal Infections, ed M McCarty, New York, Columbia Univ Press, 1954

43 Denny, F W, Jr The prophylaxis of streptococcal infections *In* Streptococcal Infections, ed M McCarty New York, Columbia Univ Press, 1954

44 Talbot, N Functional Endocrinology *from* Birth Through Adolescence Commonwealth Fund, Harvard Univ Press, 1952.

45 Lubschez, R· Identification of urinary 17 ketosteroids in rheumatic fever Pediatrics *15* 537, 1955.

46 Ely, R S., Ainger, L. E., Seely, J R., Done, A. K, and Kelley, *V C· Studies of* 17-hydroxycorticosteroids X Urinary excretion of 17-hydroxycorticosteroids in patients with rheumatic fever J Clin Endocrinol *15* 523, 1955

47 *Kelley, V. C The role of the pituitary-adrenal* system in rheumatic fever Lancet *75* 291, 1955

48 Kelley, V C, Ely, R S, Done, A K., and Ainger, L. E: Studies of 17 hydroxycorticosteroids VI Circulating concentrations in patients with rheumatic fever Am J Med *18* 20 1955

49 H[illegible] normal [illegible] 1956

[illegible] reven

50. M[illegible] ect of [illegible]

51. [illegible] nicillin in patients with rheumatic fever. J.A.M.A *138*: 103[illegible], 19[illegible]

The Treatment and Management of Rheumatic Fever

by Gene H Stollerman

THE PATHOGENESIS OF RHEUMATIC FEVER remains one of the major enigmas of modern medicine There is no specific laboratory test by which the disease may be identified Its diagnosis rests upon recognition of a clinical syndrome No specific treatment is available Despite these limitations, however, there is much that can be done for the patient with rheumatic fever There is no longer serious doubt that this peculiar inflammation develops as a complication of infection with group A streptococci The evolution of this concept has resulted in significant advances in the diagnosis, prevention and management of the disease. Furthermore, the availability of potent anti-inflammatory agents, such as salicylates and the adrenal cortical hormones, affords the means of controlling the toxic manifestations of the disease in most cases The proper administration of these agents is a valuable aid in the management of the acute rheumatic attack, even though there is as yet no conclusive evidence that the ultimate degree of cardiac damage sustained can be reduced This discussion presents some of the author's current concepts in the treatment and management of the patient with rheumatic fever It acknowledges that the limitations to our understanding of the disease process inevitably result in wide variations of therapeutic approach. No attempt at complete review of the voluminous literature on the subject is made This has been done recently elsewhere.[1,2]

ESTABLISHING THE DIAGNOSIS

The diagnosis of rheumatic fever imposes important obligations upon both the physician and patient. The proper treatment and management of acute rheumatic fever involves an intensive and expensive program of patient care and restriction of the patient's activities for periods of at least several months. The diagnosis also involves the psychological trauma that usually accompanies diagnosis involving the heart. Most important, perhaps, is that patients labeled as rheumatic subjects are obliged to maintain continuous antibiotic prophylaxis against streptococcal infection and rheumatic recurrences for many years[3]

For this reason a definite diagnosis of rheumatic fever should be reserved for those patients with a well defined clinical syndrome The modified criteria of Jones[4] for the clinical diagnosis of rheumatic fever has

72. Stollerman, Gene H The prevention of rheumatic fever, Clin. North America : 133, 1957
73 Markowitz, M . Comment on paper by Poskanzer, et al. (see ref No 3).
74 Stollerman, G H, Russoff, J. H., and Hirschfeld, I · Prophylaxis against group A streptococci in rheumatic fever patients by the use of single monthly injections of benzathine penicillin New England J. Med. *252*. 787, 1955
75 Lendrum, B L., and Kobrin, C.. Prevention of recurrent attacks of rheumatic fever J A M A *162*: 13, 1956
76 Hunter, T. H., and Paterson, P. Y : Bacterial Endocarditis Chicago, Year Book Publishers, 1956.
77 Presman, R S, Bender, I B · The concept of systemic and local antibiotic therapy in the prevention of bacteremia following extraction of teeth (abstract) Circulation *12*. 761, 1955

due to acute rheumatic fever the patient invariably will have a rising titer or a significant elevation of one of the streptococcal antibodies.[7]

Rheumatic carditis may present a different situation. A low grade carditis may exist for many months before the condition becomes apparent. It is not uncommon, therefore, to find a relatively low antistreptolysin O titer in a patient with a low grade, chronic carditis who cannot recall definitive symptoms of the exact onset of the disease.

Similarly, the patient who presents the syndrome of Sydenham's chorea sometimes does not have an elevated ASO titer because this manifestation may occur late in the course of the attack.[8] Indeed, it may occur as late as several months after the onset of acute polyarthritis when all other signs of rheumatic activity have subsided. Such cases have been referred to as "pure chorea." In the opinion of the writer, all cases of so called "pure chorea" should be regarded, at least for purposes of management, as part of the syndrome of rheumatic fever. Erythema marginatum may follow the same pattern as Sydenham's chorea. It may appear during the acute toxic stage of the disease but may also appear late in the course of the illness when the acute manifestations have apparently subsided.

From the foregoing it is apparent that the use of the antistreptolysin O titer, as well as the other commonly measured antibodies, may have definite limitations and must be interpreted with full awareness of their behavior.

For an excellent discussion of the clinical criteria for the diagnosis of acute rheumatic fever, the reader is referred to the protocol of the so-called "cooperative study" of the treatment of acute rheumatic fever in children, prepared by the Rheumatic Fever Working Party of the Medical Research Council of Great Britain and the Subcommittee of Principal Investigators of the American Council on Rheumatic Fever and Congenital Heart Disease of the American Heart Association.[9]

ANTISTREPTOCOCCAL THERAPY

There is general agreement on at least one aspect of the treatment of rheumatic fever. Group O streptococci that linger in the pharynx of the patient with acute rheumatic fever as a result of the antecedent infection must be eradicated, and new streptococcal infection must be prevented. In many cases of acute rheumatic fever, the organisms are not recovered from the throat when the diagnosis is first made. When repeated throat cultures fail to reveal the presence of group A streptococci, it is still wise to proceed as though the organisms were deep in the lymphoid tissues of the pharynx.[9] Cultures of tonsils removed from patients are often positive for group A streptococci even though prior culture of the intact mucosa of the pharynx fails to reveal these organisms.[10]

As yet there is no definite evidence that the subsequent course of rheu

proved helpful. By this scheme the manifestations of the disease are divided into "major" and "minor" categories, as follows: major—(1) carditis, (2) *polyarthritis*, (3) *chorea*, (4) *subcutaneous nodules*, (5) erythema marginatum, minor—(1) fever, (2) elevated sedimentation rate or positive test for C-reactive protein, (3) evidence of previous streptococcal infection, (4) increased P-R *interval in the electrocardiogram*, (5) *a reliable history* of rheumatic fever or definite evidence of pre-existing rheumatic heart disease

The diagnosis is considered probable if at least one major and two minor manifestations, or two major manifestations are present. It is immediately apparent, however, that the same criteria can be met by a variety of diseases that cause polyarthritis or carditis. For example, the migratory polyarthritis of early rheumatoid arthritis, particularly in the older adolescent and the adult, and the syndrome of so called benign nonspecific pericarditis may satisfy the above criteria in the early stages of illness, and only the subsequent courses of these diseases may differentiate them from rheumatic fever

For this reason the diagnosis of antecedent streptococcal infection assumes special importance. A major manifestation that follows a proved recent streptococcal infection lends considerable support to the diagnosis of rheumatic fever Conversely, when the clinical picture is equivocal the exclusion of recent streptococcal infection by immunologic studies makes the *diagnosis of rheumatic fever quite unlikely.*

STREPTOCOCCAL INFECTION IN RELATION TO THE DIAGNOSIS OF RHEUMATIC FEVER

It has been possible to demonstrate serologic evidence of streptococcal infection in almost every patient with acute rheumatic fever[5, 6] In a recent study[7] it was found that the titer of antistreptolysin O was elevated above 200 units in about 80 per cent of patients who were observed within a few months of the onset of an acute rheumatic attack. When the titer of streptococcal antihyaluronidase was also determined on the same sera, an elevation of either antibody was demonstrable in 90 per cent of patients When antistreptokinase levels were assayed on the same sera, 95 per cent of the group showed significant elevation of at least one of the three antibodies This percentage approaches 100 the earlier in the attack the patient is studied.

When further streptococcal infection is avoided by careful antibiotic prophylaxis, the level of these antibodies falls progressively, regardless of the subsequent course of the disease. It is possible to prove antecedent exposure to streptococcal infection, therefore, *only when the patient is* studied early in the course of the rheumatic attack. Acute polyarthritis occurs almost invariably early in the rheumatic attack and within a few *weeks of the antecedent streptococcal infection.* When this manifestation is

belong to other serologic groups may occasionally be relatively penicillin-resistant.[15]

Several different treatment schedules have been recommended for initiating antistreptococcal therapy in patients with acute rheumatic fever. A single intramuscular injection of 1.2 million units of benzathine penicillin, a long-acting depot penicillin salt, has been shown to achieve as high a rate of bacteriologic cure as any other course of penicillin employed for the treatment of uncomplicated streptococcal pharyngitis.[16] Such single intramuscular injections of benzathine penicillin result in low but persistent and adequate blood levels of penicillin for at least ten days.[17, 18] The same results may be achieved with more frequent injections of other penicillin salts. Procaine penicillin G in 2 per cent aluminum monostearate in oil, 600,000 units administered intramuscularly every third day for three or four doses, or daily intramuscular injections of 300,000 to 600,000 units of aqueous procaine penicillin G for ten days, may be administered as alternative therapy.[5] There is no evidence as yet that there is any advantage to these more frequent injections, and there does not appear to be any greater risk of hypersensitivity with the use of benzathine penicillin as compared to the use of procaine penicillin in comparable dosage.

Once group A streptococci have been cleared from the throat, continuous prophylaxis against new infection is instituted. A variety of methods are suitable for this purpose.[3, 15, 19] Small daily oral doses of penicillin G (200,000 units once or twice daily) or sulfadiazine (1 gram daily) may be employed. A single monthly injection of 1.2 million units of benzathine penicillin avoids the uncertainty of poor patient cooperation and has been found to be extremely effective in preventing rheumatic recurrences and new streptococcal infections. In the author's opinion this is the method of choice for continuous prophylaxis during the first two years of convalescence when the risk of rheumatic recurrences is greatest.[19] A full discussion of prophylaxis of rheumatic recurrences is presented elsewhere in this volume and has appeared in recent reviews.[19-21]

ANTI-INFLAMMATORY TREATMENT

There is no definite evidence that treatment with either salicylates or adrenocortical hormones modifies the duration of the rheumatic attack. In both instances the effect of these agents is to suppress the inflammatory process. Fever, malaise, tachycardia and other symptoms of the acute illness subside rapidly and regularly with either agent, although relief from cortisone in full doses is sometimes more certain, prompt and complete. Whether intensive suppression of cardiac inflammation results in diminished scarring of cardiac tissues is a question that is still debated. Controlled studies of fixed doses of acetylsalicylic acid, corticotropin (ACTH), and cortisone, re-

matic fever can be altered by intensive penicillin therapy once the acut rheumatic attack is under way. In the era before the widespread use of ant biotics, however, intercurrent infection with group A streptococci durin the active stage of rheumatic fever often resulted in disastrous exacerbatio of the disease. It is reasonable to assume that the persistence of streptococca infection in the rheumatic patient is likely to produce additional seriou damage The possible modifying effect of intensive penicillin therapy at th onset of acute rheumatic fever is currently under study by Dr. Charle Rammelkamp and his associates, and these investigations may provide som answers as to whether such therapy may contribute to a reduced incidenc of the severe and chronic forms of the disease.

In view of the above considerations it is now common practice t begin treatment of the rheumatic subject, as soon as the diagnosis has beer established, with a course of penicillin considered optimal to achieve bac teriologic cure of streptococcal pharyngitis or of the carrier state. For thi purpose it is necessary to administer penicillin for a minimum period o ten days Because of the exquisite sensitivity of the organisms to penicillin large doses are unnecessary Doses that maintain penicillin blood levels of more than .04 unit of penicillin per cubic centimeter of serum are quite as effective as any higher dose, provided such levels are maintained for at least ten days Higher blood levels do not result uniformly in permanent bacteriologic cure when they are maintained for any period less than ten days [11]

Occasionally one encounters a stubbornly persistent carrier of group A streptococci who is not permanently cured by a ten day course of penicillin Repeated and more prolonged courses may be necessary in such cases It is well to appreciate that the effectiveness of the action of penicillin upon sensitive organisms is determined primarily by their rate of growth The studies of Eagle[12, 13] and of Wood[14] demonstrate clearly that when penicillin sensitive organisms grow slowly they are not readily destroyed by penicillin regardless of the dose employed A common error in the treatment of the persistent carrier state is to employ increasingly large doses of penicillin in an attempt to eradicate the organisms rather than to prolong treatment with more modest doses that will provide an optimal bactericidal blood level [13] In the presence of large, chronically infected tonsils hemolytic streptococci may persist, despite repeated courses of treatment, until tonsillectomy is performed

When beta hemolytic streptococci continue to be recovered from cultures of the throat after the administration of a course of penicillin that is usually curative, it is important to establish that such organisms belong to group A and not to other serologic groups. Group A streptococci are invariably penicillin-sensitive in vitro, whereas hemolytic streptococci that

SELECTION OF ANTI-INFLAMMATORY AGENTS

Salicylates

Pending the availability of further data, it may be reasonable to employ a therapeutic approach that is adapted to the nature of the individual case It has been shown that approximately 90 per cent or more of patients with acute rheumatic fever who have no clinical evidence of carditis during the acute stage of the disease recover from the episode without evident rheumatic heart disease one year later.[9] These are usually patients with the acute polyarthritis of rheumatic fever For such patients therapy may be initiated with large doses of salicylates An initial dose of 10 grams (150 grains) of acetylsalicylic acid per day is administered to patients weighing 70 kilograms (150 pounds) or more and proportionately smaller doses are administered to patients weighing less (a convenient formula is 1 grain or 60 milligrams per pound per day) This is administered in divided doses every 4 hours Small amounts of milk taken with each dose reduce gastric irritation Large doses of sodium bicarbonate interfere with absorption and should be avoided. These doses of acetylsalicylic acid are continued until a satisfactory clinical response is obtained, that is, until the patient has complete relief of symptoms and signs of arthritis and until the temperature returns to normal range. Thereafter the dose may be reduced daily to two-thirds the initial value and may be maintained until all laboratory manifestations of inflammatory disease have returned to normal. Subsequently the dose may be reduced to one half the initial daily dose for the remainder of the course of therapy Should clinical or laboratory evidence of relapse occur when the doses are reduced, it is advisable to return to the previous higher dose that suppressed the process. Toxic manifestations are common with the use of large doses of salicylates, and these may force a reduction in the dose before the response is adequate If control of the inflammatory state is not adequate on lower, subtoxic doses, the substitution or addition of another agent should be considered. Of particular importance is the toxic symptom of hyperpnea which may be insidious and may lead to serious respiratory alkalosis and eventually metabolic acidosis if undetected Frequent determinations of serum pH and carbon dioxide content are helpful in this regard Inasmuch as the absorption of salicylates varies considerably from patient to patient, determination of salicylate blood levels is useful particularly if the patient does not appear to respond well to treatment. The usual serum level at which most patients appear to respond is between 20 and 40 milligrams per cent. Some patients have intense gastric irritation with even small doses of salicylates or develop symptoms of salicylism at relatively low blood levels In such patients aminopyrine may be employed

spectively, administered for a fixed period of six weeks, have not shown so far that any one of these agents is superior in reducing the incidence of clinically apparent rheumatic heart disease one year after termination of therapy.[9]

A parallel study in 128 adults with the same dosage[22] showed that significantly fewer new murmurs appeared in the cortisone group during therapy, and fewer murmurs that were considered "significant" were found in this group at the end of 14 months (the statistical probability of this difference was only 0.11).

These studies have been criticized by some on the basis of inadequacy of dosage and duration of administration of hormones. Several recent studies have purported to show favorable results in patients with initial attacks of rheumatic carditis treated early (within the first two weeks) in the course of the disease with very large doses of cortisone for prolonged periods.[23-25] Massell[26] has presented an exhaustive review of the literature and has included his own data to support this point of view. These studies[27] have stressed particularly the greater frequency of complete disappearance of "significant murmurs" in patients treated early in the course of the disease with large doses of hormones, as compared to a matched group treated with small doses of the same agents. Although the numbers are small and definite conclusions are not yet justified, the results have suggested to these authors that an early start, adequate duration, and adequate suppression of the inflammatory process may result in some decreased cardiac damage, at least during the early period of convalescence from the disease These possible benefits are to be weighed against the reports of others of the frequency of toxic reactions to large doses of hormones employed for prolonged periods of time[29] and to the studies that fail to indicate significant advantages of the steroids over salicylates in the prevention of cardiac stigmata.[9, 29, 30]

The striking disparity in the reported results has divided opinion sharply among many authorities regarding the value of steroid therapy in diminishing cardiac damage. It has been pointed out appropriately in editorial comment[30-32] that there is considerable need for further carefully controlled clinical trial and that a standard for therapeutic evaluation similar to that employed in the "cooperative study"[9] be employed

At the present time it appears that the absence of adequate controls, the extreme variability of the course of rheumatic fever, the limited number of cases that are seen within the first two weeks of acute rheumatic carditis, and the risks attendant in the prolonged administration of large doses of hormones have prompted caution and conservatism in the general acceptance of intensive steroid therapy for all rheumatic fever patients.

therapy employed, about 5 to 8 per cent of attacks will persist with clinically overt rheumatic manifestations for more than 6 months[7]

It is important to reduce the dose of hormone gradually over a period of about two weeks and to recognize that abrupt cessation of treatment leaves the patient in a state of temporary adrenal insufficiency due to suppression of endogenous adrenalcortical activity during prolonged hormone therapy. For this reason the relapse of acute rheumatic fever following abrupt termination of hormone therapy is frequently more severe than the initial manifestations of the disease before treatment was started It has been the policy of some to follow the gradual withdrawal of hormone therapy by several more weeks or months of administration of salicylates to assure suppression of inflammation until recovery of normal adrenalcortical function occurs[37]

Hydrocortisone may be used in place of cortisone in a dose of about ⅔ to ¾ that of the latter The recently synthesized compound, prednisone, is as effective as cortisone and has less sodium and water retaining properties[38] It is preferred, therefore, for patients with severe carditis and congestive heart failure The dosage is about 1/4 to 1/5 that of cortisone The halogenated cortisone analogues, fluhydrocortisone and chlorhydrocortisone, are about ten times as potent as cortisone per unit weight but have greater sodium and water retaining properties and are therefore unsuitable for patients with carditis Corticotropin (ACTH) is as effective as cortisone but has the disadvantage of necessitating parenteral administration It may be administered in initial doses of 120 milligrams daily by injection and gradually reduced thereafter according to the manner suggested for the use of cortisone

The relative anti-inflammatory potency of the various adrenalcortical compounds can be assayed by their ability to reverse the test for C-reactive protein (CRP) in blood.[38] This abnormal protein appears in the blood in response to a variety of inflammatory stimuli and is a sensitive but entirely non specific indicator of rheumatic inflammation[39, 40] With adequate suppression of the inflammatory process, CRP disappears from the blood within a few days to one week, and conversely, it reappears promptly when suppressive therapy is inadequate Although it usually parallels the behavior of the sedimentation rate, it varies more promptly than the latter with variations in the clinical course of the disease. Moreover, when congestive heart failure is present the sedimentation rate is often depressed to low values, whereas C-reactive protein is unaffected by this complication Its disappearance from the blood following adrenalcortical hormone or salicylate therapy is not the result of a direct effect of these agents on the metabolism of the C-reactive protein but appears to be a reflection of the effectiveness of suppression of the inflammatory process[41]

It is, in fact, a highly effective drug, equivalent in antirheumatic activity to acetylsalicylic acid at approximately one-fourth to one fifth the daily dose of the latter. The major limitation to the more general use of aminopyrine is the rare occurence of agranulocytosis. The total and differential white blood cell count should be observed, therefore, at weekly intervals when aminopyrine is employed.

Acetylsalicylic acid remains the salicylate of choice by most authorities although other phenolic compounds also have been studied. These include phenylbutazone, gentisic acid,[33] gamma resorcylate[34] and 3-OH 2 phenyl cinchoninic acid.[35] None of these substances offers a clear advantage over acteylsalicylic acid

If salicylates do not appear to provide satisfactory control of the inflammatory process there should be no hesitancy in adding or substituting cortisone or one of its analogues. It is a common observation that cortisone may provide satisfactory suppression of rheumatic inflammation in cases where salicylates cannot achieve this effect at subtoxic doses.[36]

Cortisone and its Analogues

From the foregoing discussion it is apparent that there is no absolute indication at the present time for the use of cortisone in the treatment of rheumatic fever. On the other hand the majority of authorities usually select cortisone or one of its analogues for the treatment of the patient who has clinically apparent active rheumatic carditis or a more severe form of the disease. No arbitrary dosage of the hormone can be recommended. Cortisone may be administered orally in initial doses of 300 milligrams daily (usually in 4 divided doses) until a good clinical response is achieved. Thereafter, 200 milligrams may be administered daily for several more weeks depending upon the patient's response and the severity of the disease. It would appear logical to administer enough hormone to suppress all manifestations of active inflammation, such as the presence of C-reactive protein in blood and elevation of erythrocyte sedimentation rate, as well as the acute toxic clinical manifestations, such as fever, tachycardia, and polyarthritis. As with salicylates, treatment should be maintained for a minimum period of six weeks, but the duration should be guided by the severity of the disease process and should be prolonged when signs of relapse appear upon reduction of dosage. Inasmuch as neither the hormones nor salicylates appear to shorten the course of rheumatic fever, the duration of therapy must be estimated to cover the expected course of the attack. For this reason fewer relapses are encountered when treatment is maintained for nine to twelve weeks, rather than for six weeks Approximately 75 to 80 per cent of most attacks of acute rheumatic fever will subside clinically within about 6 weeks. About 90 per cent will subside in about 12 weeks Despite the form of

be overlooked unless the physician is alert to the possibilities of its presence. Antacids are recommended routinely with the use of steroids to counteract the tendency toward gastric erosion, particularly in adults.

Should a surgical emergency arise during hormone therapy, it is important to continue the use of hormones throughout the surgical procedure and during convalescence. Daily blood pressure determinations are useful to detect the complication of hypertension. When the latter is encountered it is necessary to reduce the dose of hormone The addition of salicylates may be needed to assist in suppression of the inflammatory process

COMBINED TREATMENT WITH SALICYLATES AND HORMONES

There is little objection to the use of both agents simultaneously, and indeed some authorities advise combined therapy, arguing that maximal suppression of the inflammation by all available means may be logical The use of salicylates is of particular value during the final weeks of withdrawal of hormone therapy to aid in suppression of mild relapse of low grade rheumatic activity. Many authorities prefer to initiate therapy with one agent, however If prompt and adequate control of the inflammatory process is achieved with hormones or salicylates, there is no definite evidence yet that the addition of another agent will produce superior results.

THE USE OF DIGITALIS FOR THE TREATMENT OF HEART FAILURE

Some authorities consider that digitalis is of little value in the treatment of heart failure in patients with active rheumatic carditis and that it is, in fact, contraindicated because of the frequency with which toxic manifestations develop with its use in this situation In our own experience and that of most others, however, it has been found that digitalis usually improves cardiac function except in instances of very severe myocardial inflammation.[34] Furthermore, the use of the rapidly excreted glycosides, such as digoxin, result in the patient's prompt recovery from digitalis toxicity if medication is discontinued at the first signs of toxic manifestations It is often difficult to decide whether the appearance of an arrhythmia, such as auricular fibrillation or frequent ventricular premature contractions, is the result of digitalis toxicity or myocarditis Discontinuance of digoxin is usually followed by the disappearance of toxic manifestations within 24 to 48 hours if the disturbance is due to the drug

For the adult or adolescent of average weight, 1.0 mg of digoxin is administered initially. Thereafter 0.5 mg is given by mouth every 6 to 12 hours until a therapeutic response is obtained or until a total dose of 2.5 to 3.0 mg is administered. If no response is obtained, the dose is increased further cautiously until either improvement or toxic manifestations supervene. Once an adequate dose is given, digitalization is usually maintained

During treatment it is helpful to make weekly determinations of the *erythrocyte sedimentation rate, C-reactive* protein, hematocrit value, and white blood cell count. A variety of other so called "acute phase reactants" have also been employed to detect the subsidence or suppression of rheumatic activity. These include *tests for serum complement,*[42] *alpha globulins* precipitated with cationic detergents,[43] serum mucopolysaccharides,[44] and a variety of other nonspecific serologic reactions.

It is also useful to have electrocardiograms and teleroentgenograms weekly during treatment. The latter is particularly important to detect changes in heart size. Pericarditis is notoriously difficult to detect by physical signs alone, and it is often overlooked unless x-ray films of the chest are made at regular intervals Such films also help to reveal pulmonary infection, which may otherwise be masked by hormone therapy.

MANAGEMENT OF THE SIDE EFFECTS OF ADRENOCORTICAL HORMONE THERAPY

The undesirable side effects of treatment with corticotropin or cortisone are manifestations of excessive adrenalcortical hormonal stimulation. They consist of the following major signs and symptoms· disturbances in electrolyte, water, and carbohydrate metabolism; skin changes such as, acne, hirsutism, abdominal striae, and pigmentation; unusual fat deposition, especially around the face (moon facies), base of the neck, breast, abdomen, and hips; amenorrhea; hypertension; enlarged fatty liver; leucocytosis; and cerebral changes When treatment is discontinued, all of the side effects disappear Retention of sodium and water are most marked during the first four or five days of hormone therapy and may be diminished by restricting sodium and chloride intake sharply. This is particularly important when large doses of cortisone are administered *to patients with carditis.* In such cases it is helpful to employ special diets which have been devised to reduce the intake of sodium chloride to 200 milligrams per day.[23] Mercurial diuretics *are usually administered to patients* with congestive heart failure To compensate for possible loss of potassium, particularly when mercurial diuretics are used freely, two to three grams of potassium chloride may be given daily by mouth. The urine should be tested for sugar frequently, since diabetes, known or potential, becomes temporarily intensified and insulin requirement is increased. The diet should be high in protein to counteract the tendency to negative nitrogen balance which is sometimes induced by the hormones. Patients who are, or who have *been, emotionally* unstable or psychoneurotic should be watched closely for the development of mental and emotional disturbances It should be borne in mind that cortisone and *corticotropin have the capacity to mask* pain, and symptoms and signs of peritonitis, and to suppress fever An infectious or suppurative process may

In the author's experience the use of diphenhydramine (Benadryl), rauwolfia, chlorpromazine (Thorazine), and fever therapy have not produced an impressive response.

AMBULATION OF THE PATIENT AND EVALUATION OF SUBSIDENCE OF THE RHEUMATIC ATTACK

Regulation of the activity of the patient under treatment with anti-inflammatory drugs during the course of rheumatic fever often constitutes a problem. The clinician is frequently confronted with the patient who feels entirely well during the suppressive action of either the hormones or salicylates but who may have evidence of a mild active carditis in the form of electrocardiographic changes or changing heart murmurs that produce no symptoms. It has been our policy to keep patients in bed during the acute stage of the disease while anti-inflammatory agents are being administered How strictly bed rest is enforced, however, depends upon the severity of the attack, the degree of cardiac involvement and the effectiveness of therapy. Patients who have no clinical evidence of carditis and who respond promptly to anti-inflammatory agents are often permitted bathroom and chair privileges. Sedentary group activities and occupational therapy may be more beneficial than strictly enforced bed rest that creates restlessness and boredom. In the presence of severe cardiac involvement or symptoms of diminished cardiac reserve, a more conservative attitude toward rest is enforced

Progressive ambulation of the patient may be started when hormone or salicylate therapy is gradually withdrawn and no clinical evidence of relapse appears. This should be cautious if evidence of relapse, such as rise in erythrocyte sedimentation rate (ESR) and appearance of CRP in the blood is noted Reappearance of laboratory signs of inflammation after 6 to 12 weeks of treatment may represent but a transient relapse (the so-called "rebound") and may disappear in one to two weeks, spontaneously. If such signs persist longer, however, it is advisable to reinstitute treatment for an additional four to six weeks and to continue to restrict the patient's activity If all evidence of inflammation is absent upon the withdrawal of hormones or salicylates, the patient should continue to be observed closely, inasmuch as the disease may relapse as long as five to eight weeks later, even in the absence of new streptococcal infection Such delayed relapses that occur after withdrawal of treatment do so within four to five weeks in 95 per cent of a series of patients studied.[3] Later relapses are usually noted when advanced heart disease is present and when the subsidence of active carditis cannot be judged with accuracy. Beyond this two-month convalescent period, new attacks of rheumatic fever do not seem to occur in the absence of another streptococcal infection[1] The patient's resumption of normal activity is con-

by 0.25 to 0.5 mg. administered daily, usually in two divided doses Doses may be proportionately lower in younger children, but no arbitrary weight dose ratio is applicable for digitalization. Some children weighing 60 to 100 lbs. require the same dosage as outlined above for the adult. Throughout digitalization care is taken to administer adequate daily amounts of potassium, especially when the patient receives cortisone and when mercurial diuretics are used freely.

In evaluating the effect of cortisone or its analogues upon heart failure, it is well to remember that cardiac compensation that occurs while the patient is also receiving digitalis can be due to the latter rather than to the former.

Although patients with intractable heart failure due to a severe form of myocarditis often fail to regain cardiac compensation upon the administration of digitalis, the majority of cases show sufficient improvement so that digitalis should be employed whenever heart failure is encountered, particularly in patients with advanced rheumatic heart disease where mechanical factors contribute to the problem of cardiac decompensation When clinical signs are due solely to pericardial effusion or to severe obstruction of the mitral valve, no response to digitalis can be expected

TREATMENT OF SYDENHAM'S CHOREA

The response of the symptoms of Sydenham's chorea to the anti inflammatory reagents is difficult to evaluate because of the extreme variability of the course of this syndrome and the frequent spontaneous rapid recovery of the patient. In the author's opinion neither the adrenocortical hormones nor salicylates have been impressive When constitutional signs of rheumatic inflammation (fever, anemia, anorexia, malaise) are concomitantly present, or when carditis or other rheumatic manifestations are active, anti-inflammatory drugs should be used inasmuch as the suppression of such inflammation has a beneficial effect upon choreiform activity. This appears to be due to the fact that fever or any other type of stress aggravates choreiform activity Patients with so-called "pure" chorea, a syndrome *that often occurs* late in the rheumatic attack when inflammatory signs have disappeared,[8] fail to respond well to cortisone or to salicylates. Indeed, severe psychotic *episodes have been observed in patients with chorea* who were treated with large doses of cortisone. Although chorea may be associated with psychotic reactions in the absence of such therapy, the beneficial effects of the hormones are equivocal and they are not recommended unless concurrent carditis or systemic inflammation is present.

The course of chorea, though sometimes prolonged, is self limited. Patient nursing care, adequate sedation, the judicious use of tranquilizing drugs, and good nutrition are usually associated with satisfactory response

these low-grade productive changes are the lingering traces of a very chronic inflammatory process, but one that is not necessarily compromising myocardial function Young patients who recover from acute rheumatic bouts of severe active carditis may regain unlimited cardiac reserve within a few months despite persistent murmurs and cardiac enlargement. The probability of persistent histologic lesions in the myocardium of such patients is very great. The use of cortisone or the adrenalcortical hormones in the older adult patient with long-standing rheumatic heart disease and chronic congestive heart failure rarely results in significant benefit unless unequivocal evidence is present that the patient is suffering from a new attack of superimposed exudative acute rheumatic carditis.

SUMMARY

There is still no specific cure for rheumatic fever, but there are many therapeutic measures which may reduce the severity of the acute attack and improve the patient's chances for recovery and longevity.

Prompt eradication of Group A streptococci and continuous prophylaxis against subsequent infection with this organism is perhaps the most important single measure now available. Intensive suppression of the inflammatory process with either salicylates, the adrenalcortical hormones, or both will not terminate or shorten the disease but is quite helpful in its management The least such therapy does is to improve the patient's general condition and reduce the toxic manifestations of the disease that can be dangerous in the presence of severe carditis The evidence for a modifying effect of the antirheumatic agents upon ultimate cardiac damage is still equivocal but suggestive

The proper control of side-effects of treatment, careful management of heart failure with digitalis and diuretics, the management of the patient's activity and careful prophylaxis against new streptococcal infection are all important supportive measures

Under such management the prognosis for the patient with acute rheumatic fever has been improving steadily

References

1 Rheumatism and arthritis, review of American and English literature of recent years (tenth rheumatism review), edited by W D Robinson Ann Int Med 39 498-618, 757 906, 1953

2 Rheumatism and arthritis, review of American and English literature of recent years (eleventh rheumatism review), edited by Smyth, C. J Ann Int Med 45 831, 1956.

3 Prevention of rheumatic fever and bacterial endocarditis through control of streptococcal infections Committee on Prevention of Rheumatic Fever, Council on Rheu-

ditioned, therefore, by the degree of cardiac involvement. For the first six months after the attack competitive games or severe exertion are discouraged. Thereafter, if the heart is normal, restrictions are withdrawn. If an organic murmur is present but *the heart is not enlarged, and no signs of diminished* cardiac reserve are noted following a year's observations, restrictions are usually lifted. An exception may be the patient with pronounced aortic in*sufficiency or mitral insufficiency*. Here, evidence of severely mechanically handicapped valves warrants restriction of activity as a prophylactic measure, even in the absence of marked enlargement of the heart or diminished cardiac reserve.

Occasionally it is observed that Sydenham's chorea or erythema marginatum appears late in convalescence as an isolated manifestation, without evidence of constitutional inflammatory signs such as elevation of the ESR or appearance of CRP in blood. This may occur as long as several months after the apparent subsidence of the rheumatic attack, even in the absence of new streptococcal infection.[8] The patient should be under close observation, therefore, and examined carefully at least at monthly intervals during the first year following the attack. Thereafter, however, the appearance of chorea or of erythema marginatum has not been observed in patients receiving careful prophylaxis unless there has been a "breakthrough" of strep*tococcal infection.*[7]

About 5 per cent of patients with acute rheumatic fever develop a more chronic protracted form of the disease. Especially in those with advanced *heart disease, it is difficult to know when clinically active rheumatic* carditis has abated. It is not uncommon to note a striking improvement in general health, disappearance of tachycardia, and recovery of apparently unlimited cardiac reserve in young patients who have suffered a *prolonged rheumatic* episode and who have had longstanding rheumatic heart disease. This recovery of the functional state of the myocardium may take place in the absence of change in heart size or change in murmurs. It is a good *prognostic* sign for the end of the rheumatic attack. If recurrences are prevented in such patients, it is unusual for signs of cardiac decompensation to appear without a new rheumatic attack until many years later when myocardial failure may supervene as a result of mechanical factors. Cardiac failure that occurs later in life is most often due to mechanical factors rather than to acute rheumatic inflammation. Although histological evidence of low grade *productive in*flammatory changes are often found in the biopsied auricular appendage of patients with mitral stenosis undergoing mitral commissurotomy, such lesions are not correlated with the functional state of the *myocardium* in these patients,[45] and they are not usually associated with recent streptococcal infection.[46] They are correlated inversely with the age of the patient becoming less and less frequent in the older age groups. This suggests that

21 Denny, F. W., Jr · The prophylaxis of streptococcal infections. In Streptococcal Infections, edited by Maclyn McCarty, New York, Columbia Univ Press, 1954
22 Stolzer, B L., Houser, H B, and Clark, E J Therapeutic agents in rheumatic carditis Arch Int Med 95 677, 1955.
23. Greenman, L., Weigand, F A., Mateer, F. M., and Danowski, T S Cortisone therapy of initial attacks of rheumatic carditis Am. J. Dis Child 89 426, 1955.
24 Markowitz, M, and Kuttner, A G. The effect of intensive and prolonged therapy with cortisone and hydrocortisone in first attacks of rheumatic carditis Pediatrics 16 325, 1955
25 Done, A K, Ely, R S. Ainger, L. E, Seely, J R, and Kelley, V C. Therapy of acute rheumatic fever Pediatrics 15 522 1955
26 Massell, B F: ACTH and cortisone therapy of rheumatic fever and rheumatic carditis New England J Med 251 183, 221, 263, 1954
27 Roy, S B, and Massell, B F Comparison of large and small doses of hormones in the treatment of acute rheumatic carditis Circulation 14 44, 1956
28 Smith, R T, and Good, R A Sequelae of prednisone treatment of acute rheumatic fever Clin Res Proc 4 156, 1956
29 Harris, T N, Friedman, S, Needleman, H L, and Saltzman, H A Therapeutic effects of ACTH and cortisone in rheumatic fever, cardiologic observations in a controlled series of 100 cases Pediatrics 17 11, 1956
30 Bywaters, E. G L · Treatment of rheumatic fever Circulation 14 1027, 1956
31 Editorial Adrenocortical hormones for rheumatic fever New England J Med 255 48, 1956
32 Editorial The effect of cortisone and related steroids on the carditis of rheumatic fever Ann Int Med 44 426, 1956
33 Clarke, N E, Mosher, R E, Clarke, C N Phenolic compounds in the treatment of rheumatic fever I A study of gentisic acid derivatives, Circulation 7 247, 1953
34. Reid, J, Watson, R D, Cochran, J B, and Sproull, D H Sodium gamma resorcylate in rheumatic fever Brit M J 2 321, 1951
35 Clark, E. J, and Houser, H B Comparative effects of 3 hydroxy 2 phenylcinchoninic acid (HPC) and aspirin on acute course of rheumatic fever and occurrence of rheumatic valvular disease Am Heart J 45 576, 1953
36 Stollerman, G H Treatment in internal medicine rheumatic fever Arch Int Med 98 211, 1956
37 Fischel, E. E, Frank, C W, and Ragan, C Observations on treatment of rheumatic fever with salicylate, ACTH and cortisone Medicine 31 331, 1952
38 Dordick, J R, and Gluck, E J Preliminary clinical trials with prednisone (meti corten) in rheumatic diseases, comparative anti rheumatic potency, metabolic activity and hormonal properties J A M A 158 166, 1955
39 Anderson, H C, and McCarty M Determination of C reactive protein in the blood as a measure of the activity of the disease process in acute rheumatic fever Am J Med 8 445, 1950
40 Stollerman, G H, Glick, S, Patel, D J, Hirschfeld L, and Rusoff, J H Determination of C reactive protein in blood as a guide to the treatment and management of rheumatic fever Am J Med 15 645, 1953
41 Stollerman, G H, Glick S J., and Anderson, H C Effect of adrenocortical hormones on presence of C-reactive protein in blood Proc Soc Exper Biol & Med 87 241, 1954

matic Fever and Congenital Heart Disease of the American Heart Association Mod Concepts Cardiovas. Dis *15* 365, 1956

4a Jones, T. D.: The diagnosis of rheumatic fever J.A.M.A *126*, 481, 1944

4b Jones criteria (modified) for guidance in the diagnosis of rheumatic fever, Committee on Standards and Criteria for Programs of Care, American Heart Association Mod Concepts Cardiovas Dis *24*: 291, 1955

5 McCarty, M The immune response in rheumatic fever. *In*· Rheumatic Fever, a Symposium, edited by Lewis Thomas Minneapolis, Univ. of Minn Press. 1952

6. Stetson, C. A, Jr The relation of antibody response to rheumatic fever. *In*· Streptococcal Infections, edited by Maclyn McCarty New York, Columbia Univ Press, 1954.

7. Stollerman, G. H, Lewis, A, Schultz, I. and Taranta, A: The relationship of the streptococcal immune response to the course of acute, chronic and recurrent rheumatic fever Am J. Med. *20*, 163, 1956.

8 Taranta, A, and Stollerman, G. H: The relationship of Sydenham's chorea to infection with group A streptococci Am. J. Med *20*, 170, 1956.

9. A joint report· The treatment of acute rheumatic fever in children· A cooperative clinical trial of ACTH, cortisone and aspirin Circulation *11*: 343, 1955

10 Nelson, H G et al: Studies on rheumatic fever· Observations on tonsillar carriers of hemolytic streptococci The effect of tonsillectomy and the administration of penicillin on rheumatic and non rheumatic fever patients J Infect Dis. *38* 138, 1948.

11. Wannamaker, L. W., Denny, F W., Perry, W. D, Rammelkamp, C. H., Jr., Eckhardt, G. C, Hauser, H B, and Hahn, E. O: The effect of penicillin prophylaxis on streptococcal disease rates and carrier state. New England J. Med *249* 1, 1953.

12 Eagle, H, Fleishman, R, and Muss
tion on the therapeutic efficiency (

13 Eagle, H: *In* Evaluation of chemo
New York, Columbia Univ Press, 1949

14. Wood, W B, Jr., and Smith, M. R: An experimental analysis of the curative action of penicillin in acute bacterial infections. I The relationship of bacterial growth rates to the antimicrobial effect of penicillin J. Exper Med *103* 487, 1956

15 Stollerman, G H· The use of antibiotics for the prevention of rheumatic fever Am J Med *17*. 757, 1954

16 Chamovitz, R, Catanzaro, F. J, Stetson, C A, and Rammelkamp, C. H., Jr· Prevention of rheumatic fever by treatment of previous streptococcal infections. I Evaluation of benzathine penicillin G. New England J. Med *251*: 466, 1954

17. Stollerman, G H, and Rusoff, J. H: Prophylaxis against group A streptococcal infections in rheumatic fever patients Use of a new repository penicillin preparation J A M A *150* 1571, 1952

18 Stollerman, G. H, Rusoff, J H, and Hirschfeld, I: Prophylaxis against group A streptococci in rheumatic fever patients by the use of single, monthly injections of benzathine penicillin New Eng J. Med *252* 787, 1955.

19 Stollerman, G H· Prevention of rheumatic fever. M Clin North America (Jan) 1957, p 133

20 Rammelkamp, C H, Jr, Houser, H B, Hahn, E O, Wannamaker, L. W., Denny, F W and Eckhardt, G C. The prevention of rheumatic fever. *In*· Rheumatic Fever, a Symposium, edited by L. Thomas Minneapolis, Univ of Minnesota Press, 1952

Osteoarthritis

by Edward F Rosenberg

By tradition, treatises on osteoarthritis open with an effort to define the term, an exacting and unsatisfactory task inasmuch as the nature of this disease is poorly understood and the limits of its clinical behavior dimly outlined. Osteoarthritis has been used synonymously, in this country, with hypertrophic arthritis, degenerative, senescent, menopausal and traumatic arthritis, and with osteoarthrosis. Osteoarthritis is a form of arthritis resulting in painful disorganization of joints without accompanying evidences of inflammation or infection.

Types of Osteoarthritis Two great forms are encountered, designated primary and secondary. The primary variety may be looked upon as a true disease entity, capable of both progression and extension, and having a distinctive evolutive pattern. Secondary osteoarthritis refers to the deterioration of a joint which may develop after severe trauma or in the wake of other destructive processes such as pyogenic infections. Primary osteoarthritis is characteristically polyarticular, while secondary osteoarthritis is apt to be monoarticular. A consideration of primary osteoarthritis will occupy the main portion of this chapter.

Symptoms of Primary Osteoarthritis Pain and stiffness of joints generally appear insidiously When well established, the course is slowly progressive. Rarely, the onset is abrupt, sometimes provoked by trauma or overexertion, and in some instances the onset is without recognizable provocation When symptoms appear it may be taken for granted that the disease has been present in a quiescent phase for a long time Roentgenographic evidences of hypertrophic spur formation and even deterioration of cartilages are often well advanced when symptoms are first noted

The usual subject is elderly and overweight Osteoarthritis is by no means confined to this type of individual but may affect the thin and the underweight as well. Aside from the articular disorder, the patient may show little evidence of a systemic ailment A loss of weight is almost never attributable to osteoarthritis Muscles adjacent to affected joints do not atrophy Fever and leukocytosis are not seen Chemical constituents of the blood and sedimentation rates generally are within normal limits Anemia is not a feature of osteoarthritis, and various immunologic tests such as the sheep-cell agglutination do not show deviations from the normal. Abnormalities of general health and deviations from normal in laboratory findings should be

42. Fischel, E. E., Pauli, R. H., and Lesh, J.: Serological studies in rheumatic fever II. Serum complement in the rheumatic state. J. Clin. Invest. *28*: 1172, 1949.
43. Jacox, R. F.: The diagnostic significance of plasma protein changes in acute rheumatic fever. New York J. Med. *56*: 672, 1956.
44. Good, R. A.: Acute phase reactions in rheumatic fever. *In* Rheumatic Fever, edited by Lewis Thomas. Minneapolis, Univ. of Minnesota Press, 1952.
45. McNeely, W. F., Ellis, L. B., and Harken, D. E.: Rheumatic "activity" as judged by the presence of Aschoff bodies in auricular appendages of patients with mitral stenosis. II. Clinical aspects. Circulation *8*: 337, 1953.
46. Stollerman, G. H., Lynch, W. F., Dolan, M. A., Young, D., and Schwedel, J. B.: Immunologic evidence of group A streptococcal infection in patients undergoing mitral commissurotomy. Circulation (in press).

white. Later, atrophy may progress to a point when the cartilage is more or less completely eroded or ulcerated, leaving underlying epiphyseal bone exposed. Finally, almost complete denudation of articular surfaces may result. Whereas cartilages become atrophied and may finally disappear, boney parts actually proliferate. Increased thickness of the subchondral bone (eburnation) and overgrowth of bone at articular margins (spurs) characterize the gross changes and the roentgenographic picture of this disease. To some extent, the capsule may be frayed, and tendon sheaths become dry and adherent.

The synovial membrane plays only a minor role in this process. In some instances synovial membranes remain unaltered and hardly an inflammatory cell can be found on microscopic examination. In others, a degree of fibrosis or scarring is recognizable in the subsynovial layers. Sometimes the villous processes elongate and hypertrophy, but generally this occurs only to a minor degree in comparison with that encountered in association with rheumatoid arthritis. Cartilaginous metaplasia has been observed within hypertrophied villi. Such islands of cartilage occasionally become detached and thereafter are free in the joint space, constituting a "joint mouse" or loose-body. Various outcroppings or spurs at articular margins have the effect of interposing obstructions to normal action. Gritty or crepitant noises may be felt and heard when the joints are moved, in severe cases, affected articulations appear enlarged or gnarled. Articular swellings such as are found in patients with rheumatoid arthritis are not encountered in osteoarthritis except after unusual trauma, whereupon serous or bloody effusions may be present temporarily. Chronic effusions are not characteristic of osteoarthritis.

A remarkable and distinctive localization characterizes the lesions of osteoarthritis. Joints most frequently affected are terminal joints of fingers (Heberden's nodes). The middle group of interphalangeal joints are also susceptible but are less often affected than terminal joints. Certain segments of the vertebral column, especially the 5th, 6th and 7th cervical, and the lumbar vertebrae are often involved, while other vertebrae tend to escape. Knees, hips, acromio-clavicular joints, temporomandibular joints, joints of the instep, carpometacarpal joints of thumbs, and metatarsophalangeal joints of the great toes are susceptible. The localization of osteoarthritis is often symmetrical.

Etiology and Pathogenesis. By custom, pathogenesis of osteoarthritis has been attributed to aging and to wear, inasmuch as this disease affects elderly individuals. If, however, wear and tear are factors related to the pathogenesis, then surely other factors must also play a role. Thus, important contributing influences are thought to stem from inherited tendencies and from repeated slight injuries. An inherited pattern has been determined clearly for the form of osteoarthritis which affects terminal interphalangeal joints (Heber-

explained on other grounds. Patients with osteoarthritis
painful joints.



FIG. 1 Characteristic roentgenogram showing osteoarthritis of h
nodes of terminal interphalangeal joints with involvement of proxim
phalangeal joints Affected joints show irregular narrowing resulting
ulceration of cartilage Also various hypertrophic spurs at osseous m

Pathology. Gross and histologic changes of osteoarthri
for both the primary and secondary varieties. The lesions co
ture of changes involving cartilages, epiphyseal bones and vari
which constitute the articular capsules. Cartilages undergo a
deterioration or atrophy in the course of which the surfaces

A relationship of osteoarthritis to repeated injuries is often seen in the fact that severe osteoarthritis occurs commonly among coal miners, farmers, and persons engaged in other types of heavy labor. Other potential factors related to etiology include endocrine disorders, a defective nutritional balance and defective circulation. None of these as yet has been established as related to osteoarthritis In short, the nature of osteoarthritis is not at all understood.

Clinical Features. The onset as a rule is extremely slow, hence, patients can almost never designate a date of onset This slow, insidious course may be punctuated by more violent episodes of painful lumbago, sciatica, periarthritis of the shoulder, and torticollis For the most part, pain of osteoarthritis is mild in degree, is aggravated by use and weight-bearing and is relieved by resting. Acroparesthesias are often noted when finger joints are involved. Affected joints may appear enlarged, motions may be somewhat limited and ankylosis is almost never encountered. General health remains unaffected.



Fig. 3. Characteristic roentgenograms of patient with osteoarthritis of hip showing narrowing of articular space Hypertrophic overgrowth of acetabular margins, also sclerotic changes involving the femoral head and subchondral bone of ilium The normal alternate hip is shown for comparison

Special Localizations of Osteoarthritis

(a) Osteoarthritis of the hip (malum coxae senilis), is perhaps the most frequently encountered serious manifestation of osteoarthritis This condition

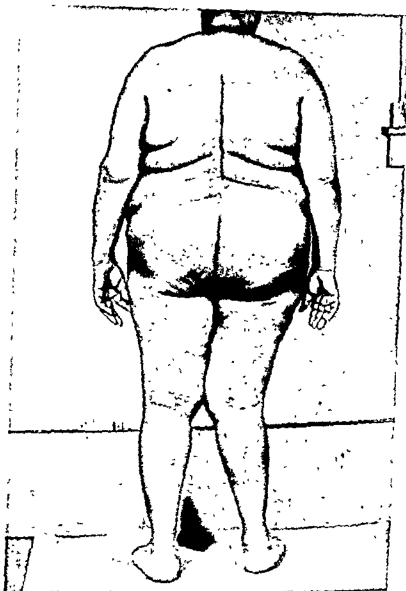


FIG. 2. Characteristic habitus of patient with osteoarthritis of spine and knees showing marked overweight, also valgus deformity of right knee resulting from atrophy of lateral meniscus of knee and other architectural changes of knee joint

den's nodes). Apparently a single autosomal gene is involved. This is sex linked, dominant in females and recessive in males. This pattern however has not as yet been shown to exist for other varieties of osteoarthritis.



FIG. 4a. Antero-posterior view of lumbar spine, showing characteristic effects of osteoarthritis. *Several disks have become atrophied and the intervertebral spaces narrowed.* Numerous osteophytes projecting from vertebral margins.

cases are encountered in which every vertebral body appears to be involved. Occasionally only a few vertebrae show advanced changes, other vertebrae remaining unaffected. In some individuals involvement of vertebrae appears

comes to the attention of patients because of pain on walking and stair-climbing. Discomfort is noted either in the groin, along the outer aspect of the thigh or about the knee. There is a tendency to develop a limp; the thigh tends to become flexed and everted. The patient often has difficulty in dressing because of inability to maneuver the extremity. Roentgenograms show the usual destructive changes, namely, narrowed, irregular articular surfaces and sclerotic thickened subchondral bone. Cyst formation is not uncommon in the diseased femoral head. Various hypertrophic spurs appear on margins of the femoral head and about the acetabulum. Hypertrophic changes may be present also on nearby bony prominences, including the femoral and ischial tuberosities, and about the symphysis pubis. The condition most often is unilateral but sometimes affects both hips.

When attention is drawn to the presence of this variety by onset of symptoms, the disease is almost invariably far advanced. Thus, little is known concerning the manner and time of onset. In occasional instances congenital malformations or acquired deformities resulting from fracture or dislocation may lay the groundwork for osteoarthritis of the hip In others no pre-existing deformity or trauma can be identified.

Malum coxae senilis differs from most other manifestations of osteoarthritis in regard to the degree of resulting incapacity. Because the hip supports the weight of the trunk and thus plays a dominant role in ambulation, loss of function of this joint causes a very serious handicap. When the process is bilateral, the result is often complete invalidism.

(b) *Osteoarthritis of Hands*. Perhaps the most characteristic and best known features of osteoarthritis are knobby ridges appearing at terminal interphalangeal joints of fingers These appear insidiously in most patients but occasionally are ushered in with an abrupt, inflammatory swelling The process may extent to involve all of the digits, and in severe instances deviations and flexions of the terminal segments may result. Not infrequently small cystlike lesions intrude into superficial layers of skin about a terminal joint. These may open spontaneously and discharge viscous or glairy fluid. Among persons showing advanced stages of Heberden's nodes on terminal joints of fingers, some develop similar enlargements of the middle group of interphalangeal joints. The proximal row or metacarpophalangeal joints are almost never affected.

(c) *Osteoarthritis of the Spine:* Some degree of hypertrophic spur formation may be found on vertebrae in almost every individual who reaches the age of fifty, and this condition becomes increasingly frequent with advancing age As in the case of osteoarthritis of other joints, such lesions are not always accompanied by symptoms, and frequently may be present for many years, reaching an advanced state of development before causing discomfort. Most often affected are lower cervical and lower lumbar segments. However, middle dorsal segments are also susceptible. In fact, far advanced



Fig. 4a. Antero-posterior view of lumbar spine, showing characteristic effects of osteoarthritis. Several disks have become atrophied and the intervertebral spaces narrowed. Numerous osteophytes projecting from vertebral margins.

cases are encountered in which every vertebral body appears to be involved. Occasionally only a few vertebrae show advanced changes, other vertebrae remaining unaffected. In some individuals involvement of vertebrae appears

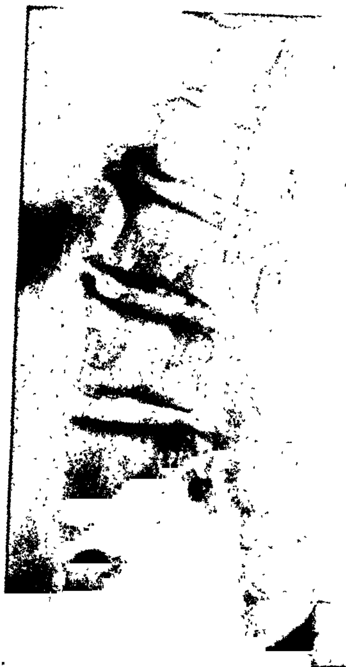


Fig 1b Lateral view of same patient showing massive hypertrophic spurs and irregularly narrowed vertebral spaces

to be unilateral, or much more severe on one side than on the other. Roentgenograms show varying degrees of alterations affecting intervertebral discs, namely, narrowing and occasional disappearance of the intervertebral space. Adjoining vertebral surfaces tend to be serrated or irregular. Various bony excrescences are formed. Osteoarthritis of the spine is often associated with osteoporosis and with changes in structure secondary to the fragility of bones resulting from this osteoporosis. Symptoms may be completely absent in some persons with well established lesions and rather severe among others who may show only minimal roentgenographic changes. Varying degrees of painful stiffness are noted when this condition causes symptoms. In some instances pain may radiate along the course of root segments, leading to confusion with various neurologic disorders. If the pain radiates to the anterior portion of the chest, angina pectoris may be suspected.

(d) *Osteoarthritis of the Knee.* This condition is never present alone, being invariably associated with other stigmata of osteoarthritis, such as Heberden's nodes, spinal osteophytes and so forth. Some individuals, however, show far advanced osteoarthritic changes in knees with relatively little trouble elsewhere. Symptoms include grating or crepitus with motion. Pain is especially marked after prolonged periods of standing and is notably aggravated by walking up and especially down stairs When the condition is well established the knee may be enlarged and complete extension may be impossible because of hypertrophic outcroppings which interfere with normal function From time to time modest amounts of fluid may accumulate, especially after unusual activities which require the patient to be on his feet a long time.

Roentgenographic findings agree in general with the usual picture of osteoarthritis. The first change is often a narrowing of the articular space resulting from atrophy of cartilage When the process is further advanced irregular sclerotic surfaces replace the usual smooth subchondral plate, bone cysts may appear in epiphyseal regions of femur, patella or tibia, and various osteophytic excresces make an appearance

Differential Diagnosis. The main problem here is differentiation between osteoarthritis and rheumatoid arthritis. Although osteoarthritis characteristically affects older persons, rheumatoid arthritis may appear during later decades of life; consequently, it is not possible to rely upon age to distinguish the two conditions. Basic differences between the two conditions should be kept in mind, especially the systemic phenomena of rheumatoid arthritis, loss of weight, anemia, various vasomotor disturbances and characteristic complications such as nodules, uveitis, and muscular atrophy adjoining affected articulations

A distinction from gout rests primarily upon the characteristic clinical

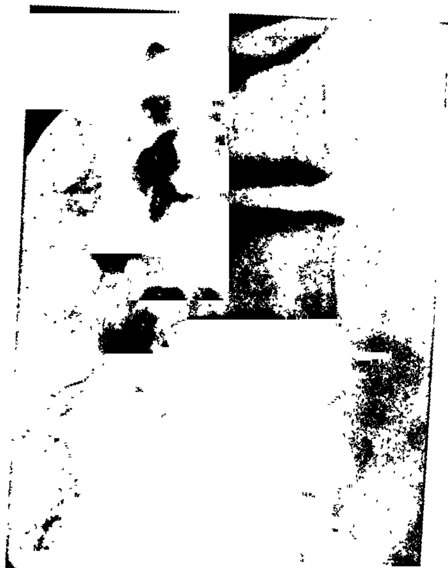


FIG. 5. Characteristic roentgenogram of patient with lumbar and lumbosacral osteoarthritis, showing huge osteophytes at lumbosacral joint apparently joined. Irregular narrowing of other intervertebral spaces with anterior and posterior osteophytes also visible.

pattern of gout, together with evidences of disturbed metabolism of uric acid

Treatment. The physician's approach to the problem of treatment for osteoarthritis should be based upon a careful appraisal of the individual as well as an estimation of the location and severity of the osteoarthritic lesions. Once joints have been damaged by this condition, restitution to normal is impossible because of a limited ability of articular structures to heal. Treatment should be directed toward amelioration of discomfort and, to whatever extent is possible, toward preventing the forward progress of articular changes

Inasmuch as no specific therapy has been evolved for osteoarthritis physicians should suggest a program of measures fitted to the individual needs of each patient. Basic ingredients of this program should consist of rest, certain physical therapy measures, adjustment of diet, medications for alleviation of pain, and certain orthopedic procedures For some aspects of osteoarthritis surgical measures may play a helpful role.

REST: Osteoarthritis does not lead to ankyloses, hence forced motions accomplish no worthwhile result On the contrary, pathologic lesions of this disease appear to originate in erosion of cartilages, a condition which is aggravated or accelerated as a result of wear and tear Therefore, rest, in a broad sense, is beneficial However, the prescription for rest should be individualized. For painful Heberden's nodes, avoidance of activities such as knitting, sewing, typing, excessive practice of musical instruments may provide worthwhile benefits For osteoarthritis of the spine, avoidance of lifting, stooping, and carrying of heavy objects should be encouraged as a method of resting the spine. For osteoarthritis of the knees and hips, avoidance of walking and climbing of stairs should be a basic element of the rest program, and at the same time consideration should be given to the question whether individual patients should be required to walk with crutches or a cane in order to further rest the affected joints. During especially painful episodes the patient should be placed at rest in bed for periods of from several days to a few weeks in order to permit almost complete rest of the painful joints Thus, no rule of thumb is available for planning the rest program for osteoarthritis Rather, this aspect of the therapy should be prescribed by the thoughtful and experienced physician in a manner appropriate for each patient. Some patients with osteoarthritis, as a result of misconceived notions regarding the disease or as a result of misguided counsel of well intentioned friends, wiggle the joints incessantly or subject themselves to various forced exercise programs in order to prevent ankylosis These exercises are potentially harmful and should be discontinued in favor of a prescribed program of rest.

PHYSICAL THERAPY Past experience has validated employment of physi-

cal therapy in the treatment of osteoarthritis. Most patients derive comfort from physical measures, including various applications of heat and massages. Manipulations and forced motions of all types should be omitted for reasons stated above. For most patients with osteoarthritis, a program of physical therapy may be arranged in a manner permitting conduct of this part of the treatment at home. Thus, inexpensive heat cradles, employing light bulbs as a source of heat, can be purchased in this country for modest sums. Warm baths, diathermy sono-therapy, applications of warm wax, packing in various heated collations, such as muds and sacks of salt or hay, have enthusiastic advocates. All of these are capable of providing a degree of comfort when employed in association with other measures of a well rounded program for osteoarthritis.

DIETARY MEASURES. Thus far no distinctive chemical disorder has been found associated with osteoarthritis and no dietary item has been incrim inated. Accordingly, manipulations of diet do not appear to be worthwhi for these patients. For overweight patients, caloric restrictions should be enforced.

MEDICAL MEASURES. Almost every patient with osteoarthritis can make good use of simple medications in order to enhance his comfort. In first place on this list of medicaments are salicylates. In the form of either aspirin or sodium salicylate, given in plain or in coated tablets, these remedies provide a degree of relief from pain without notable risk. For most adults, thre to six grams of salicylates can be tolerated daily without indigestion an without either tinnitus or deafness.

Employment of steroids as oral medication for osteoarthritis preser a considerable problem to the physician. For many patients with painful osteoarthritis, notable though temporary relief is achieved with either cortisone or other steroids. On the other hand, the basic lesions of osteoarthritis appear to be unaffected by these hormones. When these observations are taken into account, together with the fact that the general outlook for persons with this disease is good, then risks and difficulties associated with steroid therapy hardly seem justifiable The individual physician may at times secure for his patient significant relief from symptoms by administration of steroid hormones in full doses for a brief period, as for example for a few days or a week or two

Intra-articular Injections of Steroids A recently developed measure of treatment for osteoarthritis is the intra-articular injection of either hydrocortisone or meticortelone acetate. These may be injected directly into the larger joints without notable risks The results of this procedure are in general limited to partial and temporary relief of immediate symptoms. Basic programs for combatting the disease need to be worked out with each patient in addition to the procedure of intra-articular injections.

Surgical procedures. Exceptionally severe problems are encountered from time to time in the handling of patients with osteoarthritis. For some of these, surgical measures when carried out by skilled orthopedic surgeons may provide lasting benefits. Among the surgical measures which may be employed in this manner are operations for spinal fusion, patellectomy, various arthroplasties of the hip, excision of hypertrophic excrescences from knees, and excision of osteoarthritic bunions.

Fluid Effusions in Osteoarthritis. Ordinarily, effusions are not encountered among patients with osteoarthritis. Occasionally, however, generally following some unusual trauma, a moderate effusion may appear in an osteoarthritic joint. Such fluids are clear and viscous, containing relatively small numbers of leukocytes (500 to 1000 per cu. mm.). The protein content is relatively low, 2 to 3 grams per 100 cc.

Secondary osteoarthritis. Trauma sufficiently severe to damage articular surfaces may initiate scar formation. Subsequently, repeated use of such damaged joints may result in the development of osteoarthritis.

Long continued use of a pneumatic hammer for drilling may in this manner provoke osteoarthritis in wrists, about the head of the radius and about the first carpometacarpal joint. Similar changes may appear also among the small joints of the wrist and shoulder.

Degenerative arthritis, constituting in effect a form of secondary osteoarthritis, may appear prematurely in policemen, soldiers, salesmen, cooks, waiters, factory workers, nurses, dentists and others whose occupations require prolonged standing.

Joints that have been disorganized by pyogenic or other destructive infections often show severe osteoarthritis years after the infection has been overcome.

Osteoarthritis of the hip is often secondary in the sense that a preceding destructive ailment has laid the groundwork for the later appearing degenerative changes. Causes of such secondary osteoarthritis may include coxa plana (Legg-Calve-Perthes' disease), slipped upper femoral epiphyses, septic arthritis, congenital dislocations, congenital aplasia of the acetabulum, congenital anomalies of the proximal portion of the femur, coxa vara resulting from either rickets or osteomalacia, Caisson disease, and tertiary syphilis (Charcot's joints). In general, basic principles of treatment applying to these conditions are the same as those applicable to primary osteoarthritis.

Bibliography

Bayles, T B : Hypertrophic arthritis (degenerative joint disease) M. Clin North America *34* 1435, 1950

Bennett, G. A , Waine, H. and Bauer, W.: Changes in the Knee Joint at Various Ages with Particular Reference to the Nature and Development of Degenerative Joint Disease New York, 1942.

Collins, D H Osteoarthritis, J Bone & Joint Surg *35B*· 518, 1953

—— The Pathology of Articular and Spinal Diseases. London, Edward Arnold & Co., 1949.

Fletcher, E Osteoarthritis and its treatment Brit J. Phys Med *11*: 135, 1948

Freyberg, R H Osteoarthritis (Degenerative Disease of Joints, Hypertrophic Arthritis of the Aged). *In* Conn, *Current Therapy*. Philadelphia, Saunders, 1955

Ghormley, R K.. The etiology and treatment of painful hips among adult persons Surg Clin North America *23*· 946-966, 1943

Hartung, E F · Osteoarthritis and its management Bull Rheumat Dis. *1*· 13, 1951

Heberden, W . Commentaries on the History and Cure of Diseases. London, T. Payne, 1802

Hollander, J L Local effects of compound F (hydrocortisone) injected into joints Bull Rheumat Dis 2 3, 1951

Kellgren, J H , and Lawrence, J S Rheumatism in miners; x ray study Brit J Indust Med 9 197, 1952

Kuhns, J. G . Management of osteoarthritis in the aged J A M.A. *151*: 98, 1953

—— Replacement of the femoral head and other arthroplastic procedures in severe osteoarthritis of the hip Bull Rheumat Dis. 3 49 50, 1953

Nichols, E. H , and Richardson, F L. Arthritis deformans J. Med Research *21*· 149, 1909.

Parker, F , Keefer, C S , Myers, W K and Irwin, R L. Histologic changes in the knee joint with advancing age relation to degenerative arthritis *Arch Path 17*: 516, 1934

Paul, L W and Moir, W W Roentgen diagnostic aspects of chronic arthritis and bursitis Radiology *49* 6, 1946

Pommer, G Uber die mikroscopischen Kunzeichen and die Enstehungbedingungen der Arthritis deformans Virchows Arch *263* 434, 1927.

Stecher, R M Heberden's nodes, the clinical characteristics of osteoarthritis of the fingers Ann Rheumat Dis *7* 1, 1938

—— and Hersh, A H . Heberden's nodes; mechanism of inheritance in hypertrophic arthritis of fingers J Clin Invest 23 699 704, 1944

Waine, H · Osteoarthritis Bull Rheumatic Dis *6* 101, 1956

The Diagnosis of the Various Types of Osteoarthritis

by Robert M. Stecher

In discussions of Diagnoses it is important that the diseases under consideration be described and defined and that complete agreement be established concerning their characteristics. This is particularly true of osteoarthritis, a disease which has been loosely defined, frequently neglected, imitated by changes of age and accepted as one nonspecific, poorly defined clinical entity. In considering this problem one finds that it is easier to describe what osteoarthritis is not, rather than what it is. These implications may seem surprising at first thought but they are obvious and can be easily demonstrated.

Osteoarthritis is a disease usually affecting one joint, such as a knee or a hip, one pair of joints, such as the knees or the hips, or one set of joints, such as those of the fingers or the spine. This can easily be shown by careful clinical histories and physical examinations. Osteoarthritis of the fingers, or Heberden's nodes, and osteoarthritis of the hips differ in sex incidence, age of onset and relation to the menopause. It seems wise to distinguish these diseases from each other and from osteoarthritis of the knee and the spine and to talk about osteoarthritis of the fingers, osteoarthritis of the hips, osteoarthritis of the knees and osteoarthritis of the spine, instead of generalized osteoarthritis.

Evidence is first presented to show that osteoarthritis is not a general disease but is most often limited to a single joint or a single set of joints. That localizing factors are important in osteoarthritis of the hip is shown by the known effect of dysplasia of the hip, coxa plana, Perthes' disease or slipped epiphysis in causing this disease. Graber-Duvernay[1] states unequivocally that arthritis develops only in pre-existing defor[illegible] hip, and he agrees with [illegible]

[illegible]

[illegible] disease arising spontaneously with [illegible] etiology.

Examples of localized osteoarthritis of the [illegible]
C. W. was a [illegible]
the right hip [illegible]
she was sitting [illegible] graph of both hips and the pelvis taken the next day was completely normal. When seen she had well developed

arthritis. This has continued to worsen for five years, making her almost completely incapacitated She has no other arthritis. Both radiographs are shown in figure 1.



FIG 1 Two radiographs of the right hip of Mrs C W The first, at age 56, is normal The second, at age 61, shows advanced osteoarthritis with disappearance of the joint space, deformity of the head of the femur and areas of bone rarefaction producing cyst formation

Mrs. L. L, a 70-year-old woman, is incapacitated by pain, limitation of motion and flexion deformity of the right hip. This began gradually fifteen years before and has progressed slowly but relentlessly No cause of this arthritis has been found and there has been no extension to other joints

Mrs. L. M was last seen at 88 years of age, five years after she fractured her right hip and had a vitallium prosthesis replacement. Osteoarthritis of the right hip began when she was 50 and progressed without intermission. With her prosthesis she is better than she was, because even now she has no other clinical osteoarthritis.

In support of evidence that hip disease is often confined to one joint, attention is called to two gorilla skeletons described by the author,[2] one from the Anatomical Museum of the Medical School of the University of Edinburgh, the other from the Todd Collection of Western Reserve University Medical School, both showing advanced osteoarthritis of the left hips but no evidence whatever of other joint disease in the skeleton.

Osteoarthritis is often confined to the finger joints in Heberden's nodes The first patient the author studied, Mr C. R., was a man seen twenty years ago with enlargements of all the terminal finger joints His finger enlargements started in the early fifties; his arthritis had not spread to any further joint at his death at 77 years.

Mrs. B. L. noted enlargements of her fingers ten years ago, at age 42, shortly after her last menstruation. When seen she had enlargements of all her terminal finger joints (fig. 2), but no other arthritis.



FIG. 2 Mrs B L., a 52 year old woman with enlargements of all the terminal joints of the fingers which started 10 years before All terminal joints including the thumbs are involved but the proximal interphalangeal joints and the metacarpophalangeal joints are spared

In a study of a series of patients with Heberden's nodes,[3] 94 were compared to a series of 100 women of comparable ages for the presence of other arthritis, minor rheumatic complaints and joint crepitus of the knees. Twelve patients, or 12.7 per cent, had osteoarthritis of other joints, compared to 3, or 2.8 per cent, of the controls, usually in the knee. In neither group was it ever severe enough to incapacitate the patient Deformity was not marked None of these patients used a cane or a crutch. The patients were seen repeatedly over a period of years and thus had ample opportunity to complain and have their troubles recorded The control subjects were seen only once; they were not thinking of rheumatic problems when interviewed, and they perhaps overlooked or neglected similar complaints. Crepitus of the knees was noted in 36 per cent of the patients and 23 per cent of the controls It is evident that even with well marked and long standing Heberden's nodes, associated clinical osteoarthritis is rare Thus it is seen that in

many patients osteoarthritis of the hips and osteoarthritis of the fingers very often arise alone and remain unaccompanied by osteoarthritis elsewhere in the body for long periods of time.

Definite information about osteoarthritis localized in the knees is not available. Osteoarthritis of the spine, spur formation on the vertebral bodies, arises because of deterioration or degeneration of the intervertebral discs as a result of trauma The trauma in some instances may be mild and apparently insignificant, or may not even be noticed. Elderly people, invalids or cripples have marked demineralization of the bones and often sustain compression fractures of vertebral bodies instead of damage to the discs. On the other hand, young, vigorous and well trained men, such as college athletes or professional football players, sustain appalling degrees of physical abuse without harmful effects This immunity to accidents in well trained athletes is a condition recognized by athletic coaches and team trainers Arthritis of the spine develops in response to stress beyond the physiologic capacity of the tissues.

Osteoarthritis has long been considered to be a disease of advancing years, of old age or of senility. In fact, Hench introduced the term senile arthritis, but it never attained acceptance. Heine,[4] in a careful investigation with gross observation and histologic examination of many joints in 1000 consecutive autopsy cases, showed conclusively that the changes of age were similar to the changes of osteoarthritis These include cartilage wrinkling and ulceration Fibrillation and complete loss of cartilage become more common as age advances His findings were substantiated twenty years later by Bennett, Wayne and Bauer,[5] in studies of the knee.

Osteoarthritis is not of itself an indication of senility or degeneration Since it is a disease associated with permanent changes in the joint and coming on at all ages, it is obvious that the incidence increases as age advances In some individuals osteoarthritis appears early. In 100 consecutive cases of Heberden's nodes studied for the effect of the menopause upon this disease,[6] the earliest onset was recorded at 33 years in a patient whose menopause occurred five years later. Seven of these 100 patients noted Heberden's nodes before the age of forty, while 50 of them noted onset before the age of fifty years. The median age of onset was 49.1 years; the average was 48.9 years Heberden's nodes obviously is not a disease of old age, although it is common then. The same feature is shown in osteoarthritis of the hips In a series reported by Barceló[7] in 1952 of 100 cases of osteoarthritis of the hip, symptoms appeared in 4 per cent before the age of 30; the median age of onset was 52. In a series of 2100 cases of osteoarthritis of the hip reported by Graber-Duvernary, the average age of onset was found to be 57, 322 began before the age of 40. Thus it is seen that

osteoarthritis is present in advanced years, with a higher incidence in old age, but its onset often occurs in early or middle adult life, at the height of vigor and health. It usually affects one joint, one pair of joints, or one set of joints, and once present it persists for the remainder of life.

Changes occur in cartilage as age advances, changes due to wear and tear and which include thinning and perhaps even total disappearance of cartilage. Although these changes occur in osteoarthritis, other changes are present also In osteoarthritis the synovial membrane is congested and villous, and the capsule and subsynovial connective tissue is fibrotic The synovial hyperplasia and capsular fibrosis are due in part to the presence of cartilage debris shed from the joint surface and absorbed beneath the surface layer of the synovial membrane Two different processes seem to be at work, aging and osteoarthritis It seems likely that in series such as those of Heine and Bennett, Wayne and Bauer, these processes have been confused and are sometimes unwittingly intermingled. This will be inevitable until strict criteria are established to differentiate them.

Significant studies on the circulation of the femoral head and the histology of osteoarthritis of the hip were published by Trueta and Harrison[8] and by Harrison, Schajowicz and Trueta in 1953.[9] Using injection methods they showed that there is no diminution in blood supply in aged individuals and that osteoarthritis is associated with proliferation of blood vessels and increased blood supply. It is not a disease of ischemia, as it had so long been supposed to be They discuss at length the anatomy of the femoral head, pointing out that the surface of the femoral head can be sharply divided into pressure areas and nonpressure areas. Osteoarthritis is associated with the proliferation of cartilage most often and most marked in so called "nonpressure areas" This cartilage later degenerates and is invaded by advancing capillaries and larger blood vessels, resulting in absorption of cartilage and its replacement with bone Finally, there is invasion of bone by bone marrow Thus it is that spurs are formed. The authors define spurs as areas of deteriorated cartilage which have been transformed into bone. Some of these changes have been mentioned by previous students, but never before have they been so carefully described and so vividly illustrated as by these workers. The changes are adequately illustrated in their original articles

The earliest macroscopic lesion of the cartilage is loss of its normal smooth shiny surface and its replacement by an irregular one which feels softer than normal This is due to the change in the cartilage so well known and so often described as fibrillation. This change is common to both age and osteoarthritis Every femoral head over the age of 11 in their series showed this change to some degree Analysis of their material from subjects

of age 14 to 100 showed that 71 per cent of femoral heads had cartilage degeneration confined to nonpressure areas, whereas only 3 per cent had change restricted to pressure areas. In 26 per cent of the cases degeneration was shown in both areas The method of localizing the pressure from the nonpressure areas depends upon identifying the areas of dense bone trabeculation and differentiating it from areas of poor trabeculation. This indicates that normal intermittent pressure is essential for cartilage health and that lack of such pressure is harmful Cartilage in the pressure areas can be damaged by pressure which is too great or too long sustained. The formation of bone and bone marrow within degenerate articular cartilage is also shown. The cartilage of the pressure areas is well preserved. Another illustration shows a femoral head with loss of cartilage over the pressure area, while the nonpressure areas show osteophyte formation. Another specimen shows the vascular tree within an osteophyte of the medial nonpressure area An artery can be seen running superficial and parallel to the subchondral bone plate and distributing branches to the osteophyte, which grows not only toward the joint surface but also to its median extremity. Another section of a femoral head removed at arthroplasty shows how a large osteophyte has grown over the original joint surface enclosing its cartilage. Thus the original joint surface is enclosed by spur formation and a new surface has formed Illustrations such as this have been published by many authors, but they have not been heretofore satisfactorily explained. Another illustration shows radiographs of a pair of femoral heads after vascular injection. It is apparent that the bloody supply of the diseased deformed head is greater than that of the normal one Venous engorgement within the pressure segment of the osteoarthritic femoral head is shown in a slab radiograph and an angiogram.

Further evidence that proliferation of blood vessels occurs in osteoarthritis is apparent from examination of macerated skeletons of gorillas found in the Hamann Collection. In the left knee of one gorilla, extensive spur formation is found surrounding the lateral condyle attaining a width of 1 cm. in its widest area. The joint surface of this condyle shows smoothing and eburnation where it was not protected by the semilunar cartilage This area of eburnation is pierced by numberless round regular holes varying in size from 0.5 to 2.0 mm in diameter whose purpose is to allow penetration of blood vessels through the subchondral bone into the degenerating cartilage (fig 3). Similar areas are found in joint surfaces of intervertebral apophyseal joints, as well as in the upper and lower surfaces of the bodies of vertebrae surrounded by osteophytoses. The normal joint surfaces of macerated bones show a smooth velvety-looking intact surface.

Trueta et al. have demonstrated conclusively that osteoarthritis of the hip



FIG. 3 Top of a macerated specimen of left femur of a gorilla showing osteoarthritis of the lateral condyle The surface area of the joint has been substantially increased by a large surrounding spur The weight bearing area is eburnated and punctured with numberless perforations for the passage of abnormal blood vessels. This change is seen on the entire surface except small areas of the anterior and posterior surface which were protected by semi lunar cartilage The surface of the median condyle is intact, smooth and velvety appearing except for several small areas near the center The large porous area near the intercondyle eminence is an artefact where subchondral bone was torn off in maceration Top of the right femur is normal

is associated with an increase in blood supply and an invasion of blood vessels into proliferating cartilage, causing the latter to change to bone. It is possible that the osteoarthritic process, whether in the finger, the hips or the knees, is stimulated at the time of the menopause because of the known activity of the pituitary gland at this time, with elaboration of growth hormone and stimulation of cartilage growth. Added evidence to support the fact that the circulation is increased in osteoarthritis of the knee, at least, is presented by Hollander,[10] who reports that the intra articular temperature of an osteoarthritic knee is higher than that of a normal knee and of a knee affected with rheumatoid arthritis.

Thus it is seen that osteoarthritis is not a simple manifestation of old age or degeneration The changes of old age have been confused with it. Osteoarthritis is not a generalized disease, it affects one joint or one set of joints. It often arises in early adult or vigorous middle life, and its changes persist. The fundamental pathologic processes are proliferation of cartilage, the degeneration of such cartilage with invasion of blood vessels, and, finally, the transformation of this proliferated cartilage into bone and bone marrow, with the production of spurs

FINGERS

Since osteoarthritis of different joints differ so much from each other, their diagnoses will be considered separately. Osteoarthritis of the fingers,

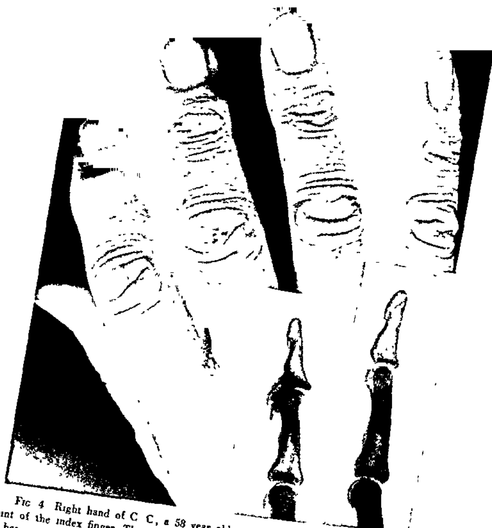


FIG 4 Right hand of C C, a 58 year old man with enlargement of the terminal joint of the index finger. This arose in response to a baseball injury 34 years before It has not changed nor spread to other fingers since Radiograms show lateral view of the damaged index finger with spur formation and the normal middle finger

or Heberden's nodes, arises in two different manners. The manifestation of the lesions themselves is usually indistinguishable, but they can be differentiated readily by the history. Traumatic Heberden's nodes arises in one finger or occasionally in two adjacent fingers promptly after a single painful injury, e g., a blow on the joint with a hammer, a finger smashed in a slamming window or door, or fingers wrenched from catching a baseball ineptly. The injury is sudden, painful, and vividly recalled as to time and circumstance, and it is followed by swelling In the course of weeks or months the swelling changes from soft, painful, edematous enlargement to hard firm, painless deformity which remains unchanged throughout the remainder of life. This is common in men, it is noted frequently in the second or third decade and increases in incidence slowly from then on Figure 4 shows the right hand of Mr C C, a 58-year-old man with enlargement of the terminal joint of the index finger This arose 34 years before, when he was hit on the finger with a baseball. It has not changed since the condition became stabilized. The radiograph shows lateral views of the damaged index finger with spur formation (Compare with the normal middle finger.)

Idiopathic Heberden's nodes arise spontaneously without known predisposing cause, starting gradually as swelling of the terminal joint of a

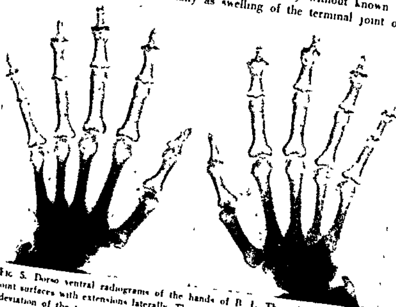


Fig 5. Dorso ventral radiograms of the hands of B L. They show distortion of the joint surfaces with extensions laterally The joint spaces are irregular and narrowed and deviation of the terminal phalanx from the straight line is seen especially in the right middle finger There is definite increase in bone mass in the distal ends of the middle phalanges.

forefinger or a middle finger, at first slightly red, tender and even fluctuant, then changing gradually in successive months to hard, nonfluctuant, nonred and nontender lesions. The course in an individual finger may take six months to two years to reach a resting stage After one finger starts to enlarge, other fingers become involved successively until often eight or all ten are affected Proximal joints may be the seat of osteoarthritis; this causes great confusion and often produces an erroneous diagnosis. In about half the cases proximal joints may be diseased, but other patients with extensive deformities of terminal joints have been followed for twenty years in whom the proximal joints have remained completely normal. Idiopathic Heberden's nodes affect women ten times as frequently as they do men, the incidence

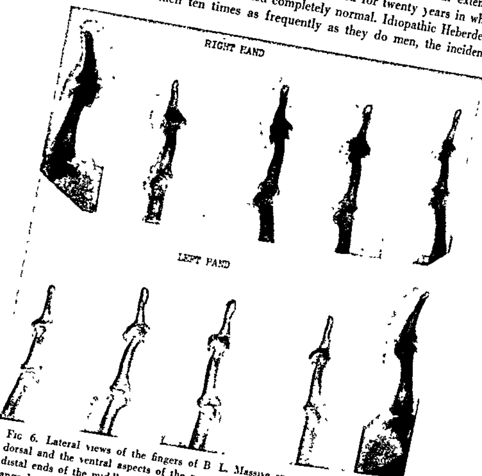


Fig 6. Lateral views of the fingers of B L. Massive spurs are seen arising from dorsal and the ventral aspects of the proximal ends of the distal phalanges and of distal ends of the middle phalanges No pathological changes in the proximal interangeal joints except for a small spur arising from the dorsal aspect of the distal of the middle phalanx of the left fourth finger.

increasing as age advances, until it reaches thirty per cent in the eighth and ninth decade. The onset is related to the menopause, since Heberden's nodes were first noted within three years of the last menstrual period in one half of the series studied Idiopathic Heberden's nodes are inherited as a sex-influenced autosomal factor dominant in women and recessive in men.

The deformities of Heberden's nodes are quite characteristic and show no regular difference in an individual finger between traumatic and idiopathic lesions First, there is *enlargement*, seen often as "two small pea sized nodules, a little to the side" of the back of the last joint, as Heberden said originally. These rounded *enlargements* may be fluctuant for months. The bone is felt to be enlarged by palpation on the ventral and dorsal aspects of the fingers. As the process advances the dorsal enlargement increases, so that the finger appears to be flexed. In the final stage, when spur formation is marked, the joint surfaces become distorted and the terminal joint is deviated laterally from the straight line The forefinger is always deviated ulnarwise, the little finger radialwise. The middle and ring finger may deviate in either direction (*fig 2*)

Radiographic studies are very instructive Figure 5 shows dorso-ventral views of the hands of B L. They show distortion of the joint surfaces with extensions laterally The joint space is often irregular and narrowed, and

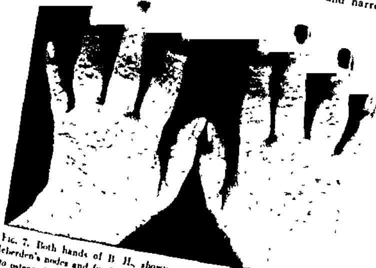


FIG. 7. Both hands of B H., showing enlargement of terminal phalanges typical of Heberden's nodes and fusiform enlargement of several proximal interphalangeal joints due to osteoarthritis The latter have been erroneously considered as typical of rheumatoid arthritis.

the deviation from the straight line is seen. The encroachment on space may be more apparent than real because of the flexion of the phalanx. There is definite increase in bone mass, apparently in th ends of the middle phalanges. The most instructive radiographs ar separately of lateral aspects of each finger. Insofar as it is possible, t should be centered over the terminal joints and the finger should b true lateral position to avoid distortion and confusing overlapping. Fig shows lateral views of the fingers of Mrs. B. L. Massive spurs are c shown arising from the dorsal and the ventral aspects of the proximal of the distal phalanges and the distal ends of the middle phalanges. T is no pathologic change in the proximal joints except for a small spur aris from the dorsal aspect of the distal end of the middle phalanx.

Contrary to earlier ideas, osteoarthritis may affect proximal inte phalangeal joints. At times these have the typical fusiform appearance s often associated with rheumatoid arthritis, as seen in figure 7. As the diseas advances the fingers become irregularly enlarged, they are deviated from the straight line, complete extension becomes impossible and flexion is limited. Patients with this involvement find it impossible to close the hand sufficiently to make a tight fist.

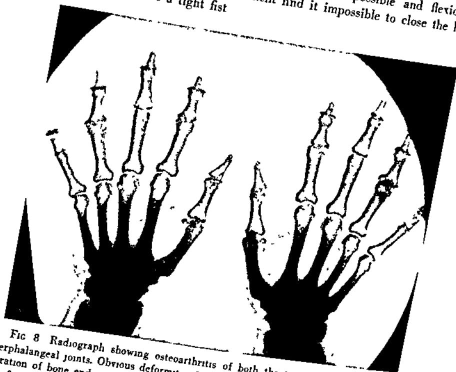


FIG 8 Radiograph showing osteoarthritis of both the terminal and the proximal interphalangeal joints. Obvious deformity of joint surfaces, decrease in joint spaces, proliferation of bone ends are particularly marked in proximal joints of the index and the ring fingers and of several distal joints. The metacarpophalangeal joints are normal.

Radiographic examination shows increased density of bone along t joint surfaces, the joint surfaces are irregular, and the joint space is uneve and narrowed, partly because of flexion deformities. Spurs are small an inconsequential. The ends of both bones may be broadened and distortec (fig 8). Osteoarthritis may involve the base of the thumb, which then becomes painful and stiff, with spurs being shown on radiographs. The author has never seen involvement of metacarpophalangeal joints with osteoarthritis, although they seem to be readily susceptible to rheumatoid arthritis.

HIPS

Osteoarthritis of the hip is a unilateral disease in about one half of the cases. It often arises in early adult life but may become apparent for the first time in advanced old age. The onset of osteoarthritis of the hip is often insidious, and, unknown to the patient, it may develop to a fully recognizable degree. Clinically, the first sign is decrease in range or nearly complete loss of rotation of the upper leg. When not associated with pain this may be completely unnoticed. As the disease advances pain becomes troublesome, flexion deformity becomes apparent, there may be outward rotation and abduction, and motion finally becomes so restricted as to serve no useful purpose. When the joint becomes fixed it also becomes painless.

The first radiologic sign of osteoarthritis of the hip is decrease of joint space and decreased radiability of the adjacent joint surfaces. As the disease progresses, the top of the femoral head becomes flattened and spurs develop along the crest of the acetabulum and at the periphery of the cartilaginous joint surfaces of the head of the femur. Bone cysts in the head of the femur in communication with the joint space in the area of contact are always seen, except in the early stages.

Two types of osteoarthritis of the hip have been distinguished by Hermodsson.[11] One depends upon underlying dysplasia which is not suspected. The head seems to move laterally, producing an increased space between the head and the vertical surface of the acetabulum. If the head remains in contact with the vertical surface of the acetabulum no dysplasia is to be suspected. As the disease advances, cartilage is destroyed and areas of increased pressure on the head develop, whether this has moved out of the acetabulum or not. The head thus becomes further deformed because of weakening of the bone structure, and collapses because of cysts. Femoral heads undergo severe degrees of deformation and absorption, producing poorer fit of the joint surface and increasing disability.

KNEES

The problems of osteoarthritis of the knee are even more obscure than those of the fingers or the hip. The changes of age in the knee have been carefully studied by Wayne, Bennett and Bauer, as they were previously by Heine. The first of these studies was confined to subjects who were

known to have symptoms or complaints referable to the joints. In this respect it may be well to quote Lloyd-Roberts,[12] who defines osteoarthritis as a clinical entity, the diagnosis of which implies the presence of symptoms and physical signs referable to a degenerating joint. Even a brief survey reveals that crepitus of the knee is a common finding in patients without complaint, the incidence of which increases as age advances. The cause of crepitus has not been well identified, but it is said to result from irregularities of the surface or of fibrillation of the cartilage. Most painful knees will produce crepitus on motion, but many people have considerable crepitus without complaining of pain or stiffness. The diagnosis of osteoarthritis of the knee should be reserved for knees with or without crepitus but in which the patient suffers pain and limitation of motion. In early stages there is lack of normal hyperextension, then lack of complete extension, and finally limitation of flexion. Knees with osteoarthritis are often slightly tender, are enlarged by thickened synovial tissues and may even contain moderate increases in synovial fluid.

Radiographic examination is often disappointing There is usually decrease in joint space due to thinning of the joint cartilage. It often is local, confined to one condyle It may be simulated, of course, by flexion deformity of the knee or even due to the radiographs being made at an unfortunate angle. Spurs are seen and are significant when attached to the posterior surface and the ligamentous attachments of the patella, where they may be large, extending centrally from the anterior joint surface of the femur. They may arise from the proximal margin of the anterior portion of the joint surface at the lower end of the femur.

SPINE

The term osteoarthritis of the spine should refer only to changes in the intervertebral apophyseal joints. These joints are subject to this disease, though the diagnosis is rarely made and is difficult to establish except in advanced cases. The disease is best known from the studies of bone collections in anatomic museums, so that the clinical features are not clear. The term osteoarthritis of the spine is also used, incorrectly, to indicate spur formation on the bodies of the vertebrae. This is not a true arthritis. Confusion and inaccuracy might be avoided if this condition is referred to as osteophytosis of the spine. According to de Séze et al.,[13] the spurs of osteophytosis and of ankylosing spondylitis are not so different as they have been thought o be Both are subligamentous ossifications arising from the edge of the ertebral body and progressing in the loose connective tissue separating the aravertebral longitudinal ligaments and the outer layers of the intervertebral sc In ankylosing spondylitis the disc is normal, it extends only to the ge of the vertebral bodies, and the spurs in this disease are confluent, regu- and slightly rounded, producing in advanced cases typical bamboo spines.

In osteophytosis of the spine, the primary lesion seems to be degeneration of the intervertebral disc with its partial displacement forward or laterally. This is due to injury or aging. Bone proliferation is thereby modified and of necessity must grow out and around the protruding discs. The protruding disc usually prevents the spurs from joining.

Because of its association with injury to the disc it is understandable that this condition is common in people who have done hard work. There is often a wide discrepancy between the size of the spurs and the history of injury or hard work, since spurs are found in people who have done little work or have sustained no known injury, moreover, they are sometimes lacking in hard working people. Work itself does not produce spurs, it is only stress and strain, however great or little, beyond the physical capacity of the individual. The well trained athlete suffers no ill effects from activities that would be harmful to ordinary people. Spurs on the spine develop in areas of compression, such as the anterior surface of the dorsal spine in patients with kyphosis or on the concave side of spines bent with scoliosis. Such spurs appear because of static compression and serve to bolster a sagging spine. In areas of the spine not subject to static pressure, spurs are found located about degenerated intervertebral discs. These can be identified since the discs are thinned, flattened, and irregular, at times protruding beyond the edge of the vertebral bodies. Spurs vary in size and distribution, from a single isolated protrusion of bone from one edge of a vertebra to a series of spurs arising from both sides and both surfaces of vertebral bodies, forming stout bridging between bodies and successfully splinting the spine to prevent motion. The largest spurs extend perpendicular to the spine, those from each side of a particular disc being nearly parallel and in contact with each other, though not fusing. If they are especially long they extend horizontally and then turn down. At other times they are short, stout and bend smoothly around a protruding edge of a disc. The descriptions given have been taken from radiographs, autopsy examinations or macerated spines. Findings as described are often entirely incidental and have not been systematic.

GENERAL REMARKS

Though osteoarthritis of different joints has been considered separately these diseases have certain features in common which tend to distinguish them from other types of arthritis. Osteoarthritis is not associated with demineralization or bone atrophy, as is rheumatoid arthritis. Osteoarthritis is not associated with constitutional symptoms. The patient is well and vigorous except for the affected joints. There are no blood or serologic changes in osteoarthritis. Osteoarthritis is often attributed to the menopause, but there is no definite evidence that the two events are related except in Heberden's nodes. Osteoarthritis is said to be caused by or to be aggravated by

obesity. In a critical study of Heberden's nodes this was found not to be so Whether or not it is true of weight-bearing joints has not been clearly demonstrated. Osteoarthritis was at one time thought to be associated with hypertension, but this idea has been abandoned.

SUMMARY

Osteoarthritis, formerly thought of as a generalized degenerative joint disease, has been shown to be a collection of particular diseases, differing from each other in joints involved, sex ratio, age of onset, relation to the menopause and hereditary factors. Osteoarthritis of the hip, the knee, the fingers and the spine may occur at any age after adolescence, and since the changes are irreversible, the incidence increases as age advances The pathologic changes have been confused with those of old age and the disease has been classed as a degenerative one. This is true of osteophytosis of the spine, which depends upon degeneration, loss of elasticity and deformity of the intervertebral discs; in the hip and knee, however, there is invasion of cartilage by new blood vessels and the transformation of cartilage to bony spurs. The intra-articular temperatures of osteoarthritic knees are higher than the normal or those with rheumatoid arthritis. Individual case histories have been given of osteoarthritis of the fingers and osteoarthritis of the hip arising in the fourth decade without extension to further joints three and four decades later. When osteoarthritis does arise from injury or hard work, it is not the injury or the hard work itself but stress and strain beyond the physiologic sustaining capabilities of the joints that institutes the pathologic process

References

1. Graber-Duvernay, J L'aspect clinique des arthrites chroniques de la hanche d'origine congenitale Revue du Rhumatisme 5 304, 1938.
2 Taylor, H W Y, King, J. B., and Stecher, R M Osteoarthritis of the hip in gorillas Report of two cases Clin Orthopaedics No 6: 149, 1955
3 Stecher, R M. Heberden's nodes· their relation to other degenerative joint diseases Arch Phy Med 27 409-413, 1946
4 Heine, I Über die Arthritis deformans Virchows Arch f path Anat. 260. 521-663, 1926
5 Bennett, G. A, Wayne, H, and Bauer, W.. Changes in the Knee Joint at Various Ages New York, The Commonwealth Fund, 1942
6 Stecher, R M, Beard, E E, and Hersh, A H · Heberden's nodes the relationship of the menopause to degenerative joint disease of the fingers J. Lab & Clin Med 34 1193, 1949
7 Barceló, P, and Santamarta, A Datos estadísticos de 100 casos consecutivos de coxartria. Rev españ de reumat. y enferm osteoart. 4· no 7, 1952.

8 Trueta, J and Harrison, M H M The normal vascular anatomy of the femoral head in adult man J Bone & Joint Surg 35B 442, 1953

9 Harrison, M H M., Schajowicz, F., and Trueta J Osteoarthritis of the hip a study of the nature and evolution of the disease J Bone & Joint Surg 35B 598, 1953

10 Hollander, J L. and Horvath, S M Effect of vaso-dilating and vaso-constricting drugs on the temperature of normal and arthritic joints Arch Phy Med & Rehab 31 162 164, 1953

11 Hermodsson, I On the roentgenologic appearance of osteo arthrosis deformans in the hip joint Acta radiol 28 257, 1947

12 Lloyd Roberts, G C. Osteoarthritis of the hip, a study of the clinical pathology J Bone & Joint Surg 37 8, 1955

13 de Seze, S., Lacapere, J., and Amoudruz, J P Osteophytes et pretendus "syndesmophytes" Vertebraux, Revue rhumat 19 107 1952.

sulted in trauma to the palm and, therefore, the contracture. The Baron described surgical correction of both these cases by dissection of the affected aponeurosis.

ANATOMY

The fascia of the palm of the hands and of the soles of the feet is quite similar (fig. 3, 4, 5). This anatomic similarity may account for a similarity in clinical conditions occurring in both these areas



FIG. 2 Knuckle pads in case of Rheumatoid Spondylitis. Biopsy of one pad showed typical rheumatoid granuloma

1. Palmar Aponeurosis (Fascia)

The palmar aponeurosis consists of a thick, triangular middle portion, which tends to thin out as it covers the thenar and hypothenar eminences. The triangular middle portion can be divided into (a) a deep thin layer composed of transverse fibers continuous with the volar carpal ligament, and (b) a superficial thick layer composed of longitudinal fibers. These longitudinal fibers are the continuation of the palmaris longus tendon. These two strata are difficult to separate since they are intimately fused and partly interwoven. These same longitudinal fibers making up the superficial layer of the palmar fascia divide into four slips upon reaching the middle of the palm. These slips blend with the sheaths of the flexor tendons and lateral ligaments of the metacarpophalangeal joints and then insert into the sides of the bases of the proximal phalanges The superficial surface of the fascia

is intimately adherent to the skin. Therefore, when a contracture occurs, there is a natural puckering of the skin, which also is one of the characteristics of Dupuytren's contracture.

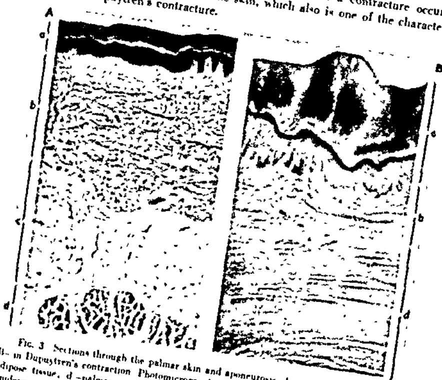


FIG. 3. Sections through the palmar skin and aponeurosis. A—in normal conditions, B—in Dupuytren's contraction. Photomicrographs (x 20). a—epidermis, b—corium, c—adipose tissue, d—palmar aponeurosis. Note in B thickening of the aponeurosis and epidermis as well as disappearance of the subcutaneous adipose layer. (Courtesy Acta Chirurgica Scandinavica, Vol. 96, T. Skoog, 1949.)

2. PLANTAR APONEUROSIS (FASCIA)

The plantar aponeurosis has tough fibrous bands which transverse and subdivide the fatty tissue into small lobules and connect the thick skin of the sole with the plantar aponeurosis. It consists of three portions: intermediate, lateral, and medial. The middle portion corresponds to the thick triangular portion in the palm of the hand and is both strong and dense, whereas the lateral and medial portions correspond to those covering the thenar and hypothenar eminences in the hand and are weak and rather thin. It is attached posteriorly to the medial process of the tuberosity of the calcaneus. It becomes broader and thinner in front and divides into five processes near the metatarsal heads. The lateral portion is thin in front and thick

behind It covers the under surface of the abductor digiti quinti and is continuous medially with the thick middle portion. The medial portion is thin and is continuously laterally with the middle portion. It covers the under surface of the abductor hallucis.

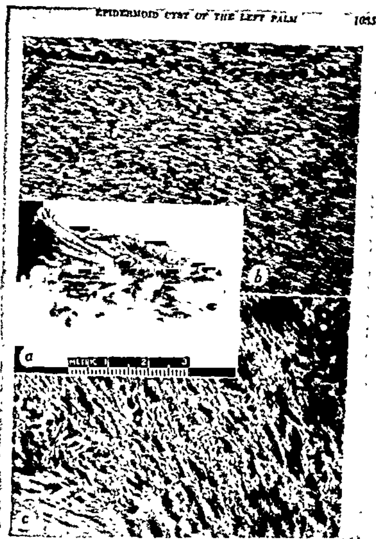


FIG. 4 *a*—Gross specimen removed from the right foot showing strands of thickened fibrotic tissue involving the plantar fascia, *b*—tissue from the fibrous mass excised from the right foot, which shows the type of cellular structure (x 150); *c*—benign proliferating cellular area in tissue from right foot; such areas have been mistaken for fibrosarcoma on microscopic examination (x 350). (Courtesy W B. Saunders Company, Meyerding, Surg. Clin. North America, Vol 28, 1948.)

INCIDENCE

Dupuytren's contracture occurs predominantly in males and is more common after the age of 40. Frequently it is bilateral. Although the palmar variety is more common, the plantar variety occurs occasionally. At times, Dupuytren's contracture is associated with a fibrositis involving the penis, in a condition known as Peyronie's disease. Table 1 shows the comparative incidence of the contracture found by various authors within the last seventy-five years.

TABLE 1 COMPARATIVE INCIDENCE OF DUPUYTREN'S CONTRACTURE

Author	Hands	Thumb	Fingers Involved: Index	Middle	Ring	Little
Keen[4] (1881)	287	11	21	73	199	165
Smith[5] (1885)	113	1	6	10	42	30
Coulhes[6] (1885)	134	3	13	47	86	70
Kanavel et al[7] (1929)	46	4	3	9	31	27
Meyerding[8] (1936)	418	21	21	88	376	314
Maurer[10] (1936)	307	—	11	97	172	130
Skoog[13] (1948)	85	11	13	34	60	65

In addition, Anderson[9] (1897) found an incidence of Dupuytren's contracture of 1.3 per cent of 2600 adult patients examined. Ayre[11] (1946) found 64 cases among 486 members of the Veterans Guard (34 were early, 25 were moderately advanced, and 2 were very markedly advanced, all were males over 40 years in age, only 1 had associated Peyronie's disease). Gordon[12] (1951) found 369 cases among 2705 patients (13.6 per cent) in 5 general hospitals. Skoog (see table 1) made the interesting discovery that 42 per cent of a series of male epileptics had Dupuytren's contracture. Scott and Scardino[14] emphasized the general nature of Dupuytren's contracture in that 6 cases of Dupuytren's contracture were found in 23 cases of Peyronie's disease. Hammond and Doter[15] (1948) described a patient with quadrilateral Dupuytren's contracture, i.e., both palms and the soles of both feet were involved. This occurred in a 40-year-old white male patient. Steinberg[16] observed a quadrilateral involvement in a young physician, aged 29. Waller and Dreese[17] (1952) described 10 patients with Peyronie's disease with associated Dupuytren's contracture. The youngest was 19 and the oldest 67. On the other hand, Mason[18] states, "Certainly my experience with several hundred patients with Dupuytren's contracture would hardly yield 2 with Peyronie's. In this connection, however, it must be said that my attention has been directed only lately to the possible association of the two conditions." In 1954, Petersen and Day[19] described three patients with Dupuytren's contracture involving the plantar fascia. These were all males, aged 26, 27, and 72, respectively. Yost et al.,[20] (1955) examined 5062 patients, 2879 males and 2183 females. Dupuytren's contracture occurred in 171 patients and in-

volved 246 hands, representing an incidence of 3.3 per cent. Of these patients, 53 per cent represented bilateral involvement, 34 per cent the right hand and 16 per cent the left hand. The average age (Table 2) in this series was 68 years, the youngest was 37, with a 15-year history. Only one instance of plantar fascia involvement was found in this series. No Peyronie's was found. In 1955, Harrison[21] described a white male carpenter, aged 46, with Dupuytren's contracture involving both the hands and feet. Arieff and Bell[22] examined 186 patients with epilepsy; of these, 32 patients, or 20 per cent, showed very mild questionable but definite Dupuytren's contracture.

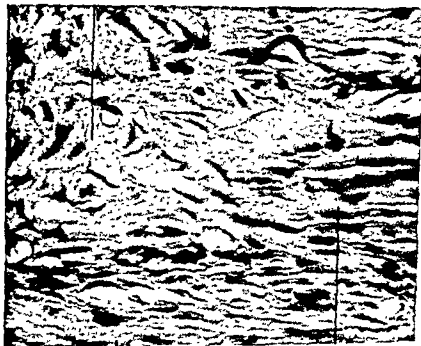


FIG 5 Section from the palmar aponeurosis in Dupuytren's contraction, showing the periphery of a cellular area of young fibroblasts (a) Note how a number of the collagen fiber bundles (b) in the aponeurotic tissue show signs of interruption in the border zone of the cellular area Stained with haematoxylin eosin (x 470). (Courtesy Acta Chirurgica Scandinavica, Vol 96, T Skoog, 1949)

SYMPTOMATOLOGY

The onset of Dupuytren's contracture may be acute or insidious. The acute onset is very rare and is usually associated with pain in the palm of the hand. By far, the most common onset is insidious. As a matter of fact, it is difficult for the patient to state just when the condition arose. Usually,

a consultation with the physician is first requested at the time at which the contracture advances to a degree sufficient to interfere with manual activities. Skoog found a high incidence of knuckle pads occurring in Dupuytren's contracture. The author, in line with the experience of others, has found no association. The macroscopic description of the knuckle pads found by Skoog could very well be that of an associated rheumatoid granuloma. Figure 2 is a radiograph of the hand of a white female, aged 43, who had knuckle pads associated with rheumatoid spondylitis. A section of this biopsy of the knuckle pads showed changes typical of rheumatoid granuloma.

A careful history will often bring out involvement of fibrous connective tissue elsewhere in the body, such as that involving the penis (Peyronie's disease), the plantar fascia, and recurrent lumbago without radiographic or physical evidence of arthritic involvement. Laboratory evidence usually obtained to indicate inflammatory reaction is absent. The sedimentation rate, white blood count, C reactive protein, and ASO titers all remained normal in this condition.

TABLE 2. AGE OF ONSET

Author	*Cases*	*Under 30*	*30-39*	*40-49*	*50-59*	*60-69*	*70-79*	*80-89*
Nichols	45	1	7	6	16	12	3	
Kanavel, Koch and Mason	29	4	6	11	5	3		
Costilhes	70	8	2	12	20	15	11	2
Scholle	51	8	9	12	15	10		
Davis and Finesilver	35	5	9	12	6	3		
Gordon	70	10	15	22	16	6	1	
Skoog	50	17	21	7	4	1		
Maurer	200	13	17	27	50	65	27	1

ETIOLOGY

At least five different causes or combinations of causes have been suggested, namely, trauma, heredity, neurologic disorder, endocrinologic disorders and altered metabolism (Table 3).

Although the traumatic theory initiated by Baron Dupuytren has been more or less adhered to by a majority of surgeons, in recent years there has been a tendency to move away from this theory, since the condition occurs in many people whose occupation (Table 4) entails little if any trauma and often involves the left hand in right handed persons. Skoog upholds the hereditary cause of Dupuytren's contracture, as do Christopher, Corletta, and Kanavel et al. Gordon[7] has reported a tabular study (reproduced below as Table 3) concerning the etiology of Dupuytren's contracture of various authors, while Table 4, compiled by Yost et al.,[8] demonstrates the condition's incidence in various occupational levels.

TABLE 3 VARIOUS DISEASES ASSOCIATED WITH DUPUYTREN'S CONTRACTURE

Disease	*Total Cases*	*Dupuytren's Contracture*
Arthritis	187	29 (16%)
Diabetes	77	20 (29%)
Tuberculosis	609	109 (19%)
Epilepsy	630	57 (9%)

TABLE 4 JOB DISTRIBUTION

GROUP I			
Machinist	4	Welder	2
Bricklayer	4	Rigger	1
Laborer	33	Roofer	1
Sheetmetal worker	4	Plumber	1
Carpenter	9	Plasterer	2
Sailor	2	Painter	6
GROUP II			
Railroad fireman	1	Electrician	1
Housewife	23	Gardener	1
Storekeeper	5	Presser	2
Machine operator	4	Barber	2
GROUP III			
Building superintendent	3	Attorney	1
Elevator operator	2	Fireman	1
Actor	1	Salesman	1
Chauffeur	2	Baker	1
Office worker	9	Letter carrier	1
Butcher	1	Watchman	1
Fruit vender	1	Dancer	1
Wool dyer	1	Messenger	1
Type setter	3	Porter	2
Hat blocker	1	Foreman	1
Waiter	1		

It is interesting that a family history was obtained in 61 out of 315 cases. Interesting also is that a review of various authors indicated that 345 patients out of a total of 634 cases of Dupuytren's contracture failed to show a traumatic factor. Moreover, of 1173 patients with Dupuytren's contracture 639 had bilateral involvement, 365 involved the right hand only, and 169 involved the left hand only.

The sex factor is important (Table 5). A study by Skoog of various authors showed that out of 118 cases of Dupuytren's contracture 103 were men and 15 were women.

TABLE 5 SEX INCIDENCE

Author	*Cases*	*Males*	*Females*
Keen	227	187	40
Anderson	39	25	14
Black	240	221	19
Byford	38	35	3
Kanavel et al	29	27	2
Davis and Finesilver	40	35	5
Noble and Silver	11	10	1
Doescher	18	17	1
Janssen	16	15	1
Costilhes	17	16	1
A A Davis	31	30	1
Gordon	51	46	5
Krogius	16	14	2
Löwy	6	5	1
Apert	4	4	0
Bathman, Sproolis	17	15	2
Stockebrandt	21	18	3
Schroder	46	40	6
Delbrunner	8	7	1

The sex distribution outlined in Table 5 corresponds with the present author's findings, since although no tabular study has been kept of the sex distribution of personal cases, it is difficult for this observer to remember many cases involving women

Steinberg[23, 24] first called attention to the use of vitamin E in the treatment of fibrositis and later speculated that since Dupuytren's contracture was a disease involving connective tissue, and hence a form of fibrositis, vitamin E might be of therapeutic value. Attention was called to the low plasma vitamin E level and patients with alcoholic cirrhosis of the liver and the association of Dupuytren's contracture in two such cases Wolfe, Summerskill, and Davidson[25] noted that "for several years the group at Thorndike Memorial Laboratories studying disease of the liver has observed Dupuytren's contracture with what seemed to be unusual frequency in patients with cirrhosis of the liver, most of whom were chronic alcoholics." They studied three groups of patients 66 with liver disease, 55 with chronic alcoholism without evidence of liver disease, and a control group of 53 patients with neither liver disease nor alcoholic histories The first group consisted of 42 males and 24 females, the second group of 49 males and 6 females and the third, a control group, of 34 males and 19 females. Sixty-six per cent of the males in the first group (cirrhosis of the liver with alcoholism) had Dupuytren's contracture Twenty-seven per cent of the males who gave an

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alcoholic history but showed no cirrhosis of the liver had Dupuytren's contracture, and only twelve per cent of the males with a history of neither alcoholism nor cirrhosis of the liver had Dupuytren's contracture. The female group was considered to be too small for statistical analysis Also, a low plasma tocopherol level was found in patients with cirrhosis of the liver, substantiating the work of Steinberg.

In summary, heredity seems to be a strong influencing factor in the etiology of Dupuytren's contracture Whereas trauma was previously considered to be the factor, most recent authors are inclined to minimize its importance Recent investigation seems to point toward an altered metabolism concerning Vitamin E as a possible etiologic factor This will be considered further under treatment.

PATHOGENESIS AND PATHOLOGY

Broadbent[26] called attention to the fact that many or all of the changes of Dupuytren's contracture could be due to a synergistic function of the sympathetic and vascular systems, since there is a definite anatomic and physiologic relation between the end organs and these systems His observation regarding the pathogenesis of Dupuytren's contracture was based on the finding that the pacinian corpuscles were found to be grossly more numerous *in twelve hands on the side of the disease. It is possible that this is an effect* rather than the cause of the condition. The most common pathologic finding in Dupuytren's contracture, whether it involves the palm or plantar fascia, *is increased fibrous tissue with almost complete absence of nuclei or cellular* infiltration (figs 3, 4) The exception to this is the rare instance of acute involvement in which a round cell infiltration along with fibroblastic-containing large nuclei were seen (fig. 3). This acute onset of Dupuytren's contracture is rather rare, and it is the type that often is associated with pain, which is practically always absent in the chronic type of involvement.

TREATMENT

Unanimity of opinion regarding successful treatment of Dupuytren's contracture does not exist The most widespread method of treatment is surgical excision of the involved palmar aponeurosis. Even within the surgical field, however, there is a wide divergence of opinion as regards the most suitable methods. Kanavel et al.,[8] (1929) recommended radical removal of the entire palmar aponeurosis and removal of the affected skin with skin grafting where necessary. Mason[18] advocates surgery, skin grafts when needed, pressure dressings, and splinting. When the dressings are discontinued at the end of the third week, home physical therapy in the form of daily washings in warm soapy water for 15 or 20 minutes is recommended. He encourages the patient to use the hand but not to punish it soon after surgery. He advises against forceful stretching. This is a rather minor report consisting of four

cases, the longest follow-up time of which being seven months. On the ot[her] hand, Matthews[27] also advocates surgery but suggests that extensor splin[ts] be worn nightly for at least three months in order to present recurrence. Gordon[12] treated his cases by surgical excision of the fascia with and without skin grafting. Forty cases were operated on and followed from one to twelve years The results were as follows: 26 excellent, 7 good, 3 fair and 3 recurrences Gray and DeTarnowsky[28] resected palmar fascia in three hands and were impressed with the difficulty in resecting the fascia in the patient with only moderate involvement Tubina[29] resected the palmar fascia in 56 hands and followed these cases from 6 months to 5 years. His results were as follows. 43 per cent very good, 34 per cent good, 20 per cent fair, and 3 per cent poor However, the reoperative cases were 14 hands out of 0 patients on which other surgeons had previously operated It is difficult search the surgical literature and not find an operator who deprecates the vious surgeon's poor results but lauds his own results This situation ap- ars to be one of the weakest links in the recommended surgical treatment of Dupuytren's contracture Langston and Cowan[30] reported the following results a recurrence rate of 10 5 per cent, 29 hands, excellent results, 47, or 38 per cent, good results, and 40 hands, or 32 per cent fair results In 9 hands, or 8 per cent, a very poor result occurred Skoog[31] reported his results under the following classifications, all treated by complete excision of the palmar aponeurosis 16 hands, grade 1, excellent results (grade 1 consisted of thickening of the palmar aponeurosis with major or minor flexion deformity of 1 finger only), 15 hands, grade 2, excellent results (grade 2 consisted of flexion deformity of more than 1 finger, nowhere attaining 60°) Of 29 cases, grade 3 (grade 3 consisted of flexion deformity of more than 1 finger exceeding 60° in at least 1 joint), 11 had an excellent result, 12 had perfect function, although the appearance was not perfect, and in 6 the result was fair. In 9 cases in grade 4 (major or minor flexion deformity of all fingers) 3 had perfect function, although the appearance was not good, and in 6 instances fair results were obtained (Skoog's over all results are shown in table 7)

Finney[11] reported on the recurrence rates of other authors (Table 6) and, because of the high recurrence rate, recommended irradiation

TABLE 6 RECURRENCE RATES

	Author	Number of Cases	Recurrence Per Cent
1	Kanavel, et al (1929)	39	35
2	Kovens (1917 1918)	30	33
3	Meyerding et al (1941)	63	17
4.	Davis (1932)	—	30
5	Ross et al (1951)	41	15

Finney reported 25 cases treated by radiation and stated that they were as successful as those treated by radical surgery, particularly in the early case. He found improvement to be maximal within 12 months. In the more advanced case, he recommended irradiation and radical surgery without fear of recurrence.

Because of the high recurrence rate after surgery and because of the known function of steroids in overcoming fibroblastic activity, it was natural that this method also be tried. Baxter and Johnson[32] noted that after operation for Dupuytren's contracture excessive scar tissue recurred. They found that 100 mg of cortisone intramuscularly daily for 1 week and then 200 mg intramuscularly daily for another week, along with whirlpool treatment and splinting, reduced the postoperative complications.

The results of complete excision of the palmar aponeurosis by various authors (Table 7) is interesting as reported by Skoog The paucity of poor results as a result of this method is not in conformity with the previous statements made in this chapter. Sixteen of these patients are reoperative cases due to recurrence Follow-up on these cases was 29 hands, 1 year; the remainder, 1 to 5 years.

TABLE 7 RESULTS OF COMPLETE EXCISION OF THE PALMAR APONEUROSIS

Author	*Hands Examined*	*Excellent*	*Fair*	*Poor*
Kanavel, et al	27	20	5	2
Wagner	20	12	7	1
Desplas Mellére	8	5	3	
Meyerding	74	55	11	8
Gerritzen	19	15	2	2
Einersson	62	43	7	12
Von Stapemohr	69	57	12	
Skoog	69	57	12	

Steinberg[23] first reported vitamin E to be of value in the treatment of early and moderately advanced Dupuytren's contracture Surgery along with vitamin E was recommended in the more advanced cases in order to prevent recurrences. Low vitamin E blood plasma levels were first reported in two patients with Dupuytren's contracture associated with portal cirrhosis Thomson[33] reported on 13 cases with involvement of 22 hands of Dupuytren's contracture treated with vitamin E He divided his cases into three groups: group A were the early cases. The diseases in this group were of short duration, and the fingers were not contracted closer than 90° The results of 10 such cases treated with vitamin E were excellent, and no surgery was required Group B consisted of the later chronic cases These all showed gross thickening of the palmar fascia, and the affected fingers were fixed in the palm Eight such cases benefited from vitamin E therapy In four such cases, surgery along with vitamin E was the method of treatment Group C consisted of old operated cases with recurrences. There were

four such cases, and the process of recurrence was halted with vitamin E therapy. In two cases extension was regained. Scardino and Scott[34] noted the association of Peyronie's disease with Dupuytren's contracture and obtained successful treatments with vitamin E. Kirk and Chieffi[34] administered vitamin E to 19 patients, 14 males and 5 females, with 26 contracted hands. One of these patients also had Peyronie's disease. The treatment consisted of 300 mg of alpha tocopherol daily for 300 days and then a follow-up for 1 year after stopping vitamin E. A novel method of determining the concavity of the palm of the hand was described, with marked lessening of the concavity as a result of disappearance of a contracture. On the other hand, Richards[35] treated 46 cases of Dupuytren's contracture with vitamin E and noticed no improvement in any case. Further studies of the association of disurbance of vitamin E metabolism and Dupuytren's contracture is of some interest. Klatskin and Krehl[36] corroborated Steinberg's work in finding that the rise in plasma tocopherol concentration following the oral administration of d-1-alpha tocopherol acetate was significantly smaller in liver disease subjects than in hospital controls. Studies by Wolfe et al.[25] have extended the studies associated with vitamin E. They found low plasma vitamin E levels in patients with alcoholic portal cirrhosis of the liver. It might be argued that the percentage of people in this study showing Dupuytren's contracture—12 per cent—with a history of neither alcoholism nor cirrhosis, is unusually high. On the other hand, it must be remembered that these were patients in the wards of the Boston City Hospital whose diet must be generally considered to be inadequate. Whether or not one accepts the thesis that vitamin E is beneficial in the treatment of Dupuytren's contracture, the fact remains that there is enough evidence to show both the low vitamin E blood level in people with cirrhosis of the liver and the strong association between this condition and Dupuytren's contracture.

SUMMARY AND CONCLUSIONS

The etiology of Dupuytren's contracture is not known. The preponderance of opinion is that heredity plays a role in its etiology. In recent years, trauma has been considered to be less and less important as an etiologic factor. That faulty vitamin E metabolism plays a role in its causation has not been universally accepted. However, it remains an interesting field of investigation to determine the exact role of metabolism of the tocopherols in Dupuytren's contracture. The neurologic factor, an etiologic modus operandi, also remains rather obscure. It is difficult at the present time to determine whether or not the changes in the pacinian bodies are the result rather than the cause of Dupuytren's contracture. Regarding treatment of the condition, surgical excision is still the most popular method of approach to the problem, although the recurrence rate is much higher than the more enthusiastic surgeons' reports.

References

1 Plater, F.· Observationum Liber, *1*: 140, 1614 (quoted by Skoog).
2. Cooper, Sir A · Quoted by Skoog (see ref 13).
3 Dupuytren, G : Permanent retraction of the fingers Lancet 2. 222, 1834
4. Keen, W. W : The etiology and pathology of *Dupuytren's contracture of the fingers* Philadelphia Medical Times *12*: 370, 1881
5 Smith, N. Seventy cases of Dupuytren's contracture of the palmar fascia Brit M J *1*: 275, 1885.
6 Costilhes, J De la retraction de l'aponerose palmaire (Maladie de Dupuytren). Paris, These, 1885.
7. *Anderson, W. Deformities of the Fingers and Toes. London, 1897 (cited by Nichols).*
8 Kanavel, A. B., Koch, S L., and Mason, M. L.: Dupuytren's contracture, Surg Gynec. & Obst *48* 145, 1929.
9 *Meyerding, H. W.· Dupuytren's Contracture. Arch. Surg 32. 320, 1936*
10 Maurer, G · Zur Lehre der Dupuytrenschen Palmartascienkontraktur und ihre Behandlung. *Deutsche Ztschr. Chir. 246. 685, 1936.*
11 *Ayre, W. B : Dupuytren's Contracture. Canad, M. A. J 54: 158, 1946*
12. Gordon, S . Dupuytren's contracture, the significance of various factors in its etiology Ann Surg. *140* 683, 1954
13. *Skoog, T Dupuytren's contracture Acta chir. Scandinav. 96· 1, 1948.*
14 Scardino, P. L, and Scott, W W · Use of tocopherols in the treatment of Peyronie's disease Ann New York Acad Sc. *52*. 390, 1949
15 *Hammond, G, and Dotter, W. E: Quadrilateral Dupuytren's contracture Guthrie* Clin. Bull. *18*· 34, 1948
16 Steinberg, C. L.· Scientific Exhibit, New York M Soc Annual Meeting, Buffalo, *N Y, May 5, 1947.*
17 Waller, J. I and Dreese, W C Peyronie's Disease associated with Dupuytren's contracture· J Urol. *68* 623, 1952
18 *Mason, M. L.· Dupuytren's contracture Arch. Surg. 65· 457, 1952*
19 Pedersen, H E and Day, A. J · Dupuytren's disease of the foot. J A. M A *154*: 33, 1954
20 *Yost, J, Winters, T, and Fett, H C., Jr.: Dupuytren's contracture. Am J Surg 90:* 568, 1955
21 Harrison, M H M Dupuytren's contracture of hands and feet. Proc Roy Soc. Med *48 164, 1955*
22 Arieff, A J and Bell, J Epilepsy and Dupuytren's contracture *Neurology 6*· 115, 1956
23 *Steinberg, C L · New method of treatment of Dupuytren's contracture·* a form of fibrositis. M Clin North America *30*: 221, 1946
24 Steinberg, C L Tocopherols in the treatment of primary fibrositis Arch. Surg *63*· 824, 1951
25. Wolfe, S J., Summerskill, W H J, and Davidson, C. S: Thickening and contraction of the palmar fascia (Dupuytren's contracture) associated with alco*holism and hepatic cirrhosis* New England J. Med *255*· 559, 1956
26 Broadbent, T. R.: Dupuytren's contracture. observations on the pathology Rocky Mountain M J *52*· 1087, 1955
27. Matthews, D N . Dupuytren's contracture. Practitioner *169*. 641, 1952

28. Gray, G. A. and De Tarnowsky, G. O., Dupuytren's contracture. U. S. Armed Forces M. J. *1* 49, 1950.
29. Tubiana, R. Prognosis and treatment of Dupuytren's contracture. J. Bone & Joint Surg. *37A*. 1155, 1955
30. Langston, R. G. and Cowan, R. J.: Dupuytren's contracture. a survey of cases five years after operation. J. Int. College Surg. *23* 710, 1955
31. Finney, R. Dupuytren's contracture, a radiotherapeutic approach. Lancet *2* 1064, 1953
32. Baxter, H. Johnson, L., Madder, V., and Schiller, C. Cortisone as an adjunct in the treatment of postoperative stiffness of the hand. Canad. M. A. J. *63* 540, 1950
33. Thomson, G. R. Treatment of Dupuytren's contracture with vitamin E. Brit. M. J. *2* 1382, 1949
34. Kirk, J. E. and Chieff, M. Tocopherol administration to patients with Dupuytren's contracture. effect on plasma tocopherol levels and degree of contracture. Proc. Soc. Exper. Biol. & Med. *80* 565, 1952
35. Richards, H. J. The surgical treatment of Dupuytren's contracture. J. Bone & Joint Surg. *36B*. 90 1954
36. Klatskin, G. and Krehl, W. A. The significance of the plasma tocopherol concentration and tocopherol tolerance tests in liver disease. J. Clin. Invest. *29* 1528, 1950

The Shoulder-Hand Syndrome

by Otto Steinbrocker and Thomas A. Argyros

THE SHOULDER-HAND SYNDROME is a symptom complex characterized by painful disability of the shoulder. It may be followed, accompanied, or preceded by painful disability of the corresponding hand and fingers where vasomotor disorders and *swelling occur, which may terminate in dystrophic changes* and contractures.[56, 55] Frequently, the opposite shoulder is affected and, occasionally, both hands. The clinical picture is a manifestation of a group of disturbances occurring in the upper and lower extremities called "reflex neurovascular disorders" It frequently is termed reflex "sympathetic" dystrophy, but in fact there appears to be so diverse an upheaval of the neural and autonomic supply to the affected parts that any single role is not completely supported by the present state of our information. The term dystrophy refers to the peculiar nutritional changes of the skin, underlying tissues and adjacent articulations, arising presumably as a result of the neural and circulatory disturbance over a long period of time. With progression of the disorder, the "dystrophic" alterations represent an advanced residual phase *of the process which is unpredictable at the onset in any given case*

The neurovascular disorders are designated as "reflex" because they have been provoked by, or appear to be the aftermath of surgical, orthopedic or medical conditions. The clinical pictures are known as causalgia, Sudeck's atrophy, post-traumatic osteoporosis, painful disability of the shoulder following *coronary occlusion, postinfarctional sclerodactylia, palmar and digital* contractures, as well as Dupuytren's contracture, the swollen atrophic hand associated with cervical osteoarthritis, certain changes in the paretic limbs of hemiplegics as well as a number of others. Analysis of the reports on these symptom-states makes it apparent that, although the conditions underlying these various *syndromes are different, the clinical features as well as the* neurovascular and other mechanisms producing them are similar, if not identical [10, 14, 21, 23, 25, 30, 38, 39, 44, 45, 47 59, 60]

We have described a small group of patients in whom no definitive provocative or related basis could be demonstrated for their "reflex" neurovascular manifestations [56] *These "idiopathic" cases continue to occur in a* fairly high proportion of our observations. They may represent our more severe criteria for incriminating "provocateurs." "Idiopathic" does not imply that no provocative or underlying basis exists but it merely means that in those patients recognizable etiologic factors could not be demonstrated

At times only partial or *localized reflex symptoms of the complete* shoul-

der-hand syndrome may occur in limited or isolated form, without further extension at the shoulder or at the hand, as listed in table I

TABLE 1

REFLEX NEUROVASCULAR DISORDERS OF THE UPPER EXTREMITY

Clinical Forms

LOCALIZED

1 Contractures of the palmar fascia and Dupuytren like contracture.
2 Painful vasospasm or vasodilatation of finger(s)
3 Swelling and atrophy of the hand (and fingers)
4 Painful disability of the shoulder

EXTENSIVE

1 The shoulder hand syndrome

Such circumscribed involvement occasionally precedes more widespread features or it may develop slowly It may progress rapidly at a single site or at multiple areas In some cases, even such localized reflex disorders may leave residual changes Reflex neurovascular phenomena and symptoms of the lower extremity often occur, but a symptom-complex analogous to the shoulder-hand syndrome involving the legs has not been observed by us.

CLINICAL CHARACTERISTICS AND COURSE

For diagnostic and prognostic convenience, the disorder may be divided into three stages [56]

The first stage of three to six months duration (figs. 1 and 2) is manifest by the onset of pain, limited motion and diffuse tenderness of one or both shoulder girdles The symptoms are followed, or may be preceded, by the acute onset of uniform, relatively nonpitting edema of the dorsum of the hand and of the fingers The hand is dusky or pink at first, but later may be pale The skin over the hand and fingers becomes smooth and taut when the normal wrinkles and creases are obliterated. The affected hand generally is warmer than the other but the grip is weak. Mobility of the finger joints is limited, and passive manipulation of the fingers is painful with the hand and fingers held in slight flexion. Mild to exquisite tenderness throughout the hand and fingers is provoked by palpation Pain may arise only from efforts at motion or palpation, or it may be a spontaneous, continuous aching, occasionally of a burning quality Only in exceptional cases do external factors, such as temperature changes, noise or vibration, aggravate the symptoms

The second stage is characterized by the gradual relief of the painful shoulder dysfunction and by resolution of the swelling of the hand. Stiffness and flexion deformities of the fingers may relax, become fixed or even more pronounced. The subcutaneous tissues and intrinsic muscles of the hand show evidence of a peculiar atrophy, the "trophic" or "dystrophic" changes Even rolling up of a localized area of the palmar fascia or incipient Dupuytren-like contractures may appear. Early trophic skin changes and coldness of the

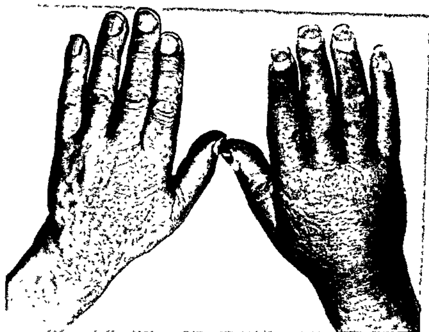


FIG 1 *Stage 1* Classic features at shoulder and hand; desquamation of skin at hand; trophic changes of nails seen occasionally (Accompanying and following herpes zoster of neck, shoulder and arm)



FIG 2 *Stage 1* Bilateral shoulder-hand involvement, completely responsive to therapy in 6 weeks; without recurrence 3½ years later (Idiopathic).



FIG 3. *Stage 2, early*. Swelling of hand and fingers largely resolved, finger function restricted (Idiopathic)



FIG. 4. *Stage 2, advanced*. Contractures of fingers with persistent swelling reflecting an active process potentially responsive to therapy, trophic changes of skin present (*Probably due to foraminal encroachment*)

hand and fingers become increasingly noticeable (figs. 3 and 4). By this time, patchy or groundglass osteoporosis of the hand, especially at the wrist and at the head of the humerus becomes evident in x-ray films. The roentgenologic alterations may appear with remarkable rapidity. In one of our patients typical, extensive demineralization of the bones of the hand was visible in a film taken 48 hours after the onset of symptoms.

The third stage follows in three to six months with even more progression of the trophic appearance of the hand which represents a terminal or residual phase of the syndrome. The skin has become increasingly smooth, glossy, and tight, with further loss of creases and gradual thinning of the cutis Trophic changes may appear in the nails. Hypertrichosis often occurs at the dorsum of the digital phalanges and even of the hand. The hand may become cooler with further interosseous muscle atrophy. Fibrous (?) ankylosis seems to "freeze" the digital articulations with subsequent severe limitation of motion at all joints. Contractures of the flexor tendons frequently occur and subluxations may develop. In the most severe cases residual disability of the shoulder persists (figs 5 and 6). The joint spaces are not visible in x-ray films, largely due to the flexion changes. A telescoping of all stages in a rapid progression to terminal dystrophic changes occasionally is encountered. In the final phase the temperature differences, signs of vascular disturbance as well as subjective symptoms gradually vanish, leaving in their wake the residual dystrophy. It should be emphasized that not every patient presents all of the characteristic features mentioned. Furthermore, reflex dystrophy may become arrested with partial or complete spontaneous resolution at any stage.

TABLE 2
SHOULDER HAND SYNDROME
PROVOCATIVE OR ASSOCIATED CONDITIONS
146 cases

	No	*Per Cent*
Idiopathic	33	23
Post Infarctional	30	20
Cervical-Discogenetic or Intraforaminal Spurring	29	20
Post-Traumatic	15	10
Multiple, Inconclusive	16	11
Post Hemiplegic	9	6
Miscellaneous	14	10
Post-Herpes Zoster	3	
Calcific Tendinitis of Shoulder	2	
Pancoast Type Tumor	3	
Diffuse Vasculitis	2	
Brain Tumor	2	
Febrile Panniculitis	1	
Gonococcal Arthritis	1	



Fig 5 *Terminal stage* 4 years after myocardial infarction, and onset of shoulder-hand symptoms, *untreated*, *residual disability of shoulder and hand*



Fig 6 Dupuytren like contracture of palms with trophic changes and residual contractures of digits (Post infarctional)

ETIOLOGY

The shoulder-hand syndrome, or any of the reflex neurovascular disorders of the upper extremity, may be due to, or associated with, a variety of "benign," provocative or associated conditions listed in table 2. Whether the coincidental presence of some "pathologic" condition necessarily implies an activating relationship often is not clearly ascertainable by clinical methods The relationship and role of some abnormalities presumed to produce reflex dystrophy, such as for example, degenerative disc changes in the cervical spine or encroachment upon one or more cervical foramina by osteophytes, remain to be evaluated by clinical observation of more material and the effects of surgical correction on the reflex symptoms

There undoubtedly are many more activating diseases or causes of the shoulder-hand syndrome than have been recorded. Any visceral, musculoskeletal, vascular or neural pathology is a potential source of reflex neurovascular symptoms Frequently, reflex disorders are overlooked in the presence of the more serious and difficult problems. Early reflex neurovascular reactions may resolve spontaneously. In many cases, however, with serious causative disease, even such as myocardial infarction, the reflex phenomena may so rapidly progress in severity and disability as to overshadow the underlying condition in diagnostic and therapeutic importance

In our series females have predominated somewhat (57 per cent); while 90 per cent have been over 50 years old Nearly every variety of occupation has been represented, with only a small number of individuals engaged in strenuous work Almost every national origin in our cosmopolitan population has been included, negro as well as white.

PATHOPHYSIOLOGY

At present there is no satisfactorily proved physiologic mechanism. Some of the present concepts of the rationale of this disorder are theoretical. Others are based on experimental or clinical evidence, or on a combination of these approaches It cannot be stated that any explanation now available accounts for all of the features and variations observed in our series of cases We, therefore, may summarize current concepts as previously discussed by us.

Studies on the dynamics of this complex largely have concerned those related to trauma They have consisted of attempts to explain the obvious vasomotor changes and the distinctive types of pain encountered in the post-traumatic syndrome. The peripheral, injured area has been accepted as the site of origin of afferent stimuli with the sympathetic system as the efferent branch of the reflex. According to the growing impression, external trauma constitutes only one source of reflex dystrophy, while internal tissue violence or damage is encountered more frequently in our material and in the reports of other observers. As we have stated, the syndrome arises from many dif-

ferent causes A more inclusive physiologic clarification, therefore, is in order It must take into account these pertinent clinical facts (1) conditions of widely separated location, such as myocardial infarction, herpes zoster, peripheral injuries, etc., can cause practically the same clinical picture, (2) this disorder seems to involve not only the autonomic system, parasympathetic as well as sympathetic, but also the sensory and motor pathways, (3) the disturbance does not show a definitely segmental distribution; and (4) it is often improved or abolished by interruption of the sympathetic nerve supply to the upper extremity.

Any working explanation of the reflex mechanism remains hypothetical to a great extent, since it must depend on current concepts in neurophysiology, each of which cannot be completely verified by experimental or clinical methods to the exclusion of the others An abundant literature supports the idea of an axone reflex and or of antidromal stimulation from a focus of irritation or injury. However, the probable role in this syndrome of the internuncial pool, as developed by Lorente de No and elaborated by Livingston, appears to offer the clearest understanding of its dynamics in many of the cases.[32, 33] The clinical picture seen in the shoulder-hand syndrome embraces a medley of signs and symptoms which must be effected through the autonomic and cerebrospinal outflows of several cervical and thoracic spinal segments. The afferent stimuli may be assumed to arise in a general way from a focus of physiologic irritation or from a local, injured area in the extremity, the heart, the cortex, etc , which may involve any site of external disturbance or violence to tissue.

In many cases, as for example, in cerebral lesions, the afferent stimuli must enter cord segments far removed from those supplying the upper extremity Owing to this fact and to the rather diffuse nature of the signs in the shoulder-hand syndrome, the segments involved usually defy accurate neurologic localization. The mechanism can be readily conceived, however, as a widespread disturbance of the internuncial pool Recent neurophysiologic investigation shows this pool to be an extensive network of interconnecting neurones in the central gray matter, extending over many segments At these levels potential connecting pathways are formed between incoming impulses and motor neurones of either the sympathetic (posterolateral) or anterior horn cells

The internuncial disturbance may be visualized as arising in this manner following a myocardial infarction, for example afferent stimuli traverse the cardiac nerves to enter the cord at levels T_1-T_4 These new and critical stimuli strongly activate the internuncial pool in that area of the cord The disturbance spreads upward with affects on the anterior horn cells, causing disability of the shoulder muscles It travels downward to involve the sympathetic neurones of the lateral horn cells innervating the upper extremity

The continuous activity of the internuncial pool and the chronicit shoulder-hand condition may be due to self-exciting, and self perp closed chains established at various points in irregular fashion, as c by Lorente de No. The severity of the symptoms would depend or tensity of the stimuli and rate of discharge of the chains of irritati diffuse involvement upward and downward of spinal cord segment account for the fact that specific myotomes and dermatomes do n to be selectively affected in this syndrome rather than a good par upper extremity, as we find.

The next consideration in discussing the mechanism of reflex d must be the beneficial results obtained from local interruption of t pathetic system Many of the clinical features clearly point to a neuro imbalance, predominantly of the vasomotor system. In the first s the disturbance the hands are apt to be warm and swollen The eleva face temperature ordinarily is acknowledged to indicate an increase flow. Confirmatory evidence of this principle has been advanced Takats[10, 11] in his observations on post-traumatic dystrophy. He r that oscillographic pulsations are augmented but at the same time ple graphic records show an increased flow in the affected extremity. El Weiss[14] studied hemiplegias complicated by the features regarded by the shoulder-hand syndrome. They found in most of them, by measu of arteriovenous differences, that the blood flow was increased on tl trophic side.

In the later stages of the syndrome a different type of vasomot turbance is present. The hand is generally cold with the skin appearii and atrophic Ischemia completes the evidence of vasoconstriction Le believes that trauma produces an instability of the autonomic nervous which may lead to alternating and intermittent stages of vasoconst and vasodilatation Either of these vascular phenomena, in his opinioi persist as a chronic disorder.

In the later stages of the shoulder-hand syndrome, with the on trophic changes and diminished temperatures, the reason for the l from sympathetic block is fairly obvious. As a matter of fact, howevei results are obtained in the first phase, when the hand is warm and al shows evidence of an increased blood flow but the use of nerve block seems paradoxical. Miller and de Takats found that after sympathetic the already augmented blood flow on the dystrophic side was furth creased. These aspects of the underlying physiologic mechanism re further clarification.

The osteoporosis, which may develop rapidly, probably represen initial result of the hyperemia found in the early phase but it has long known that bone atrophy follows any prolonged, deep hyperemia. It i

likely that the decalcification found in this condition arises merely as a disuse atrophy. Disuse atrophy due to general decalcification takes a much longer time to appear than the short interval peculiar to the disorder under discussion. Moreover, the osteoporosis of reflex dystrophy, as Sudeck first noted, is observed to develop in limbs that are functioning, especially the lower extremities.[51]

The pain of the shoulder-hand syndrome, particularly in the post-traumatic variety, is attributed to stimulation of regular pain afferents in the vicinity of the traumatized or damaged area. It must be recalled, however, that an autonomic disturbance appears to be part of the "vicious circle" which maintains a state of irritability at the the termination of the pain receptors, possibly by altering local metabolites, in that way leading to continuous stimulation or "bombardment" of the internuncial pool of the spinal cord.[52] When the efferent elements of this circuit, especially the sympathetic fibers, are interrupted, the "vicious circle" often is broken and its attendant pain abolished. The relief of disability and muscle spasm following sympathetic block in these cases may be explained on the same basis. Despite the paradoxical features, difficult to clarify entirely in the present state of our knowledge, the fact remains that interruption of the sympathetic nerve supply to the limb relieves pain, resolves the signs and restores function in many cases, at least temporarily, with impressive rapidity.

The effectiveness of corticosteroids and ACTH is less easily correlated with physiologic concepts of the disturbance. The relief of pain may derive in part from the well-being and euphoria fostered by these compounds. Further analgesia may arise from the local effects on cellular metabolism, the absorption of edema, its compressive action and any associated cellular or inflammatory-like reaction.

The cellular pathology of the shoulder-hand syndrome is unknown, so a complete elucidation of the probable action of corticosteroids at the involved sites is not possible at this time. Reports on biopsies of periarticular tissues at the shoulder suggest a low-grade inflammatory reaction with proliferation of fibrous tissue, similar to findings in the periarticular structures of non-specific periarthritis or "frozen shoulder." Biopsies of the palmar fascia of a Dupuytren-like contracture* and of the skin and muscles of the fingers of two other patients with advanced shoulder hand syndrome have yielded no distinctive microscopic observations.

DIFFERENTIAL DIAGNOSIS

It is important for many reasons to distinguish reflex dystrophy of the upper extremity from other conditions it may resemble. Because the reflex signs in the limb may happen to be those first noticed, before the evidence

*Courtesy of Dr. Wallace Graham, Toronto.

of causative disease in the thoracic viscera, brain, cord or regional musculoskeletal structures, their early, correct interpretation assumes great diagnostic importance. From a therapeutic standpoint the effective, undelayed use of proper measures and the avoidance of strenuous treatment, employed in the diseases with which reflex dystrophy may be confused, make differential diagnosis an especially imperative consideration.

Each phase of the evolution of the shoulder-hand syndrome presents similarities to various musculoskeletal conditions requiring differentiation. It is important, of course, at all stages to recognize the nature of the "reflex" symptoms in this syndrome, because they may be the clue to a provocative underlying process The disease most frequently simulated is rheumatoid arthritis. The chief features distinguishing the shoulder-hand syndrome from rheumatoid disease are the involvement of one upper extremity (except when it is bilateral), the typical sites affected in characteristic progression, the diffuse involvement of the fingers rather than being restricted to the digital articulations and the normal sedimentation rate, unless other coincidental pathology or metabolic disturbance accelerates erythrocyte sedimentation. In our series only six patients described pain at the elbow and in three of these there was limited mobility of that joint at the affected extremity.

In the evolution of the shoulder-hand syndrome, the early stage of reflex shoulder involvement, particularly when acute and subacute resembles bursitis and periarthritis (periarticular fibrositis). The local signs—pain (sudden or insidious), diffuse tenderness and disability in all ranges of motion—are similar to those seen in the uncomplicated intrinsic disorders of the shoulder, bursitis, tendinitis and periarthritis. If a calcific deposit, however minute, happens to be visualized, calcific tendinitis or bursitis is apt to be diagnosed. When a history of trauma to the extremity, visceral disease or evidence of severe cervical intraforaminal encroachment is presented, the probability of incipient or localized reflex dystrophy must be suspected, appearing in many cases as the forerunner of the complete clinical picture. The onset of hand signs should eliminate any doubt and completes the evidence of the shoulder-hand syndrome. In patients with prolonged shoulder disability scapulo-humeral fixation seems to develop, just as in the intrinsic shoulder entities. When the hand is affected with diffuse swelling, particularly with the typical edematous induration of the dorsum, acute arthritis or gout is strongly suggested The shoulder-hand syndrome is unresponsive to a therapeutic trial of colchicine. The indurated swelling of the skin of the fingers and hand in the shoulder-hand syndrome may resemble the appearance of sclerodactylia, notably when both hands are affected Shoulder involvement preceding, accompanying or following the hand signs is not observed in that localized variant of scleroderma

In the later phases of the syndrome, chiefly when shoulder symptoms have resolved, apart from rheumatoid arthritis, sclerodactylia is most closely simulated. The developing digital contractures emphasize such an impression. In the terminal stage the same diagnosis is apt to crop up. At this time, "arthritis" is suggested; rheumatoid, by the dystrophic changes and digital contractures; "mixed" arthritis by the same alterations associated with Heberden's nodes which are exaggerated by the soft tissue atrophy. Residual dystrophic changes and contractures limited to a few fingers may resemble a terminal neuropathy. There rarely are any abnormal neurologic responses in the extremity of the shoulder hand syndrome, apart from hyperesthesia of the skin of the hand in the early stage.

MANAGEMENT

General Considerations

The treatment of this condition at present cannot be based on any entirely satisfactory specific therapeutic agent. Numerous methods of therapy have been advocated here, as for other reflex neurovascular disorders. Our observations suggest that the earlier the condition is recognized and treated the more responsive it is apt to be. Therapeutic or surgical violence is detrimental. Pain always is an indication for treatment but, beginning at Stage two, structural alterations are likely to be increasingly unresponsive or irreversible, in direct proportion to their duration and extent.

Any underlying or associated condition should be treated according to its own requirements. Any deficiency which lends itself to correction should receive due attention in order to improve the patient's general physical state. Pain may require supplementary analgesics until the complete treatment program has been worked out and effectively instituted. Salicylates in large amounts, 6-8 grams daily in divided doses, may provide some palliation. Codeine or other narcotics may become necessary for temporary relief of acute symptoms. Sedation usually is desirable.

Therapeutic Procedures of Possible Value

Physical modalities may give temporary palliation but our observations have not confirmed any impressive or definitive influence on the course of the condition.

X-ray therapy to the affected shoulder and extremity has been the subject of contradictory reports.[20, 42] Our experience in three patients receiving x-radiation to the cervicodorsal area and its sympathetic ganglia was unimpressive.

Local analgesic injections of "trigger-points" or *"tender points"* at the shoulder or other parts of the extremity may prove effective at sites of trauma when performed early.[4] Diffuse soreness develops so quickly at the shoulder

or abolition of pain) in another 50 per cent Minor residual defects have persisted in an impressive number of our patients during respectable therapeutic benefits, chiefly in those not seen in early phase. Occasionally, in severe, refractory cases, not too far advanced, sympathectomy is justified and likely to prove effective. Three sympathectomies were performed in our series

There is a definite place for a new therapeutic agent superior to the best methods now available. In fact, much remains to be known about the clinical enigma termed the shoulder-hand syndrome (and its synonymous disorders), particularly the pathophysiology and pathology.

PREVENTION OF THE SHOULDER-HAND SYNDROME AND REFLEX NEUROVASCULAR DISORDERS

Although the mechanism by which reflex symptom reactions are produced may not be clear in some cases, clinical and experimental observations suggest some preventive measures worthy of application In traumatic conditions, myocardial infarction, discogenetic and osteophytic encroachment on cervical foramina, hemiplegia and herpes zoster in which 5 to 20 per cent of the patients have been reported to develop reflex complications, precautionary measures, within the limits of the patient's tolerance and the facilities available, seem to be worthy of careful introduction Preventive steps to be considered, according to the circumstances in each case are

1 The recognition and evaluation of intercurrent, atypical or different pain, with or without disability, at a shoulder or hand following trauma, internal disease, previous disorder or disease of the extremity

2. Avoidance of casts, splints or manipulation in the management of painful symptoms associated with neurovascular features.

3 Gently graduated exercises, whenever feasible and tolerable at the shoulders and hands of patients suffering from lesions known to provoke reflex syndromes.

4. Injection of definite local "trigger point"(s) with procaine solution in traumatic or post traumatic disorders, especially in the presence of suggestive reflex neurovascular symptoms

5 Adequate treatment of any related or provocative pathology, such as disc lesions, or vertebral osteophytosis, anginal syndrome, etc.

References

1 Askey, J M The syndrome of painful disability of the shoulder and hand complicating coronary occlusion Am Heart J 22 1-12, 1941

2. Barcelo, P, and Juncadella Ferrer So-called shoulder-hand syndrome in myocardial infarction Rev Espan Reum 2 490-487, 1948.

3 Bayles, T B, Judson, W E, and Potter, T A: Reflex sympathetic dystrophy of the upper extremity (Hand shoulder syndrome). J A M A *144* 537 542, 1950
4 Berger, H The treatment of post myocardial infarction shoulder hand syndrome with local hydrocortisone Postgrad. Med *15*: 6. 1954
5 Bouvram, Y and Bidoux, L · Cortisone therapy in the shoulder hand syndrome Revue Du Practicien 4 (30). 2845-7, 1954
6 Carrol, I N, and Mahru, M Shoulder-hand syndrome following coronary heart disease Delaware State M J *22* 52-54, 1950
7 Chapius, R On a case of atypical shoulder hand syndrome Schweiz med. Wchnschr *88*. 1543, 1953
8 Chitwood, W R Shoulder-hand syndrome complicating myocardial infarction South M J *44*· 72-75, 1951
9. Chitwood, W R Importance of recognizing post-infarctional shoulder hand syndrome New England J Med *243* 813 814, 1950
10. de Takats, G, and Miller, D. S Post traumatic dystrophy of the extremities—chronic vasodilator mechanism Arch Surg *16*. 469-479, 1943
11 de Takats, G Causalgia states in peace and war J.A M A *128*. 699 704, 1945
12 Dozier, G S · The shoulder hand syndrome J. Kentucky State M. A *51* 441-8, 1953
13 Dubois, M The shoulder hand syndrome, its etiology and therapy Schweiz med Wchnschr *84*. 994-6, 1954
14 Ellis, L B and Weiss, S Vasomotor disturbances and edema associated with cerebral hemiplegia Arch Neurol & Psychiat. *36* 362 372, 1936
15. Evans, J A Sympathectomy for reflex sympathetic dystrophy, J A M A *132* 620 623, 1946, Reflex sympathetic dystrophy· report on 57 cases Ann Int Med *26* 417-426, 1947
16 Findlay, T, and Patzer, R The treatment of herpes zoster by paravertebral procaine block J.A M A *128* 1217, 1945
17. Gilsanz, V, Martinez, J B and Tamames, C Shoulder hand syndrome Rev Clin Espan *39* 81-91, 1950
18 Girald, P F, Allegre, G E and Lanternier Neurovegetative disorders of shoulder and hand developing after thoracoplasty. Rev. Neurol *84* 55 57, 1951
19 Gurd, F B Post traumatic acute bone atrophy—a clinical entity Arch Surg *32* 273-291, 1936
20 Hermann, L G, and Caldwell, J A Diagnosis and treatment of post traumatic osteoporosis Am J Surg 511-630, 1941
21 Hermann, L G, Reineke, H G, and Caldwell, J A Post-traumatic painful osteoporosis a clinical and roentgenological entity Am J Roentgenol *47* 353-361, 1942
22 Hilker, A W Shoulder-hand syndrome, complication of coronary artery disease Ann Int Med *31*· 303-311, 1949
23 Homans, J Minor causalgia a hyperesthetic neurovascular syndrome New England J Med *222* 870-874, 1940
24 Jespersen, K.· Cervical sympathetic block in periarthrosis of the shoulder joint with secondary reflex dystrophy Ann Rheum Dis *8*. 220 222, 1949
25 Johnson, A C Disabling changes in the hand resembling sclerodactylia following myocardial infarction Ann Int Med *19*· 433-456, 1943
26 Kammerling E, Lewis, G N, and Ehrlich, L.: Recurrent post-infarctional shoulder-hand syndrome New England J Med *242* 701-702, 1950
27 Kauther, R · On the shoulder-hand syndrome in heart disease Med Klin *48* 1750, 1953

28 Kelly, M Chronic rheumatic diarthroses and shoulder-hand syndrome M J Australia *1*: 330-334, 1953
29 Leriche, R The Surgery of Pain Baltimore, Williams & Wilkins, 1939
30 Legrand, R and Desruellas, J Coronary syndromes and scapulohumeral periarthritis Echo Medical Du Nord *24* 313 9, 1953
31 Laine, V A Incidence of reflex sympathetic dystrophy of the upper extremity, the shoulder hand syndrome Ann Rheumat Dis *12* 4, 315-6, 1953
32 Livingston, W K Pain Mechanisms a Physiologic Interpretation of Causalgia and its Related States New York, Macmillan, 1943
33 Lorente de No, R Analysis of the activity of the chain of internuncial neurons J Neurophys *1* 207, 1938
34 Losada, M., and Zanartu, J The shoulder hand syndrome Rev clin Españ *50* 298 304, 1953
35 Luhan, J A Hemiedema in cases of hemiplegia Arch Neurol & Psychiat *36* 42 57, 1936
36 Mauvoisin, F, and Bernard, J The shoulder hand syndrome Toulouse med *55* (6) 597-603, 1954
37 Michele, A A Scapulo costal syndrome, its mechanism and diagnosis N Y J Med *55* 2485 93, 1955
38 Miller, D S, and de Takats, G Post traumatic dystrophy of the extremities Sudeck's atrophy Surg, Gynec & Obst 75 558-581, 1941
39 Mitchell, S W, Morehouse, G R and Keen, W W Gunshot Wounds and Other Injuries of Nerves Philadelphia, Lippincott 1864
40 Moberg, Eric The shoulder hand-finger syndrome Acta chir Scandinav *109* 284 92 1955
41 Morgensen, E F Reflex vasodilatation test in patients with periarthrosis humeroscapularis and the shoulder hand syndrome Acta med Scandinav *145* 1 14, 1953
42 Mumford, E. B Roentgentherapy in acute osteoporosis—a new type of treatment J Bone & Joint Surg *20* 949, 1938
43 Munch Peterson, C J The so called shoulder hand syndrome Nordisk med *51* 291 3, 1954
44 Noble, T P, and Hauser, E Acute bone atrophy Arch Surg *12* 75 94, 1926
45 Oppenheimer, A The swollen atrophic hand Surg, Gynec & Obst *67* 446-454, 1938
46 Pojer, J, and Ninger, E On atypical cases of the shoulder hand syndrome following myocardial infarction Cardiologia *24* 215 24, 1954
47 Powers, H Dupuytren's contracture one hundred years after Dupuytren interpretation J Neurol & Ment Dis *80* 386-409, 1934
48 Prewitt, G Symposium on pain in the neck, shoulder and arm The role of sympathetic influence Portland Clin Bull *8* 111 20, 1955
49 Reg, L Reflex dystrophy of the arm, a case treated with ganglioplegics Jornal Do Medico *22* 570, 1953
50 Robecchi A The shoulder hand syndrome Reumatismo 7 153 79, 1955
51 Russek, H I, Russek, A S, Doerner A A and Zohman, B Cortisone in treatment of shoulder hand syndrome following acute myocardial infarction Arch Int Med *91* 487-492, 1953
52 Schesfly, C H Shoulder pain and coronary heart disease Proc Staff Meet Mayo Clin *29* 363, 1954
53 Schlegel, H Shoulder hand syndrome due to coronary insufficiency, 2 cases. Kreislaufforsch *41* 839 915, 1952.

54 Sigler, J. W., and Ensign, D. C: ACTH and cortisone in the treatment of the shoulder-hand syndrome J Michigan M. Soc *50*. 1038-1044, 1954
55. Soulie, P., Tricot, R, and De Georges. Shoulder-hand syndrome and aortico-coronary disorders Semaine d hôp Paris *26*. 4141-4150, 1950
56 Steinbrocker, O · Painful homolateral disability of shoulder and hand with swelling and atrophy of hand Ann Rheum. Dis *6*: 80, 1947, The shoulder hand syndrome Am J. Med *3* 402, 1947; Ann. Int. Med *29*. 22-52, 1947
57. Steinbrocker, O. The Shoulder-hand syndrome Post-Grad. Med *16*. 47-57, 1954
58 Steinbrocker, O, Neustadt, D, and Lapin, L.· The shoulder-hand syndrome Sympathetic block compared with corticotropin and cortisone therapy J A M A. 9 788-91, 1953
59. Sudeck, P · Ueber die akute enzundliche Knochenatrophie. Arch. f klin Chir *62*. 147 156, 1900
60 Sudeck, P Ueber die akute reflektoris knochenatrophie nach Entzunden und Verletzungen an den Extremitaten und ihre klinische Erscheinungen Fortschr. a d geb Rontgenstr *5* 277 293, 1901.
61 Swan, D M Shoulder hand syndrome following hemiplegia Neurology *4*. 480 2, 1954.
62 Swan, D M, and McGowan, J M Shoulder-hand syndrome following myocardial infarction, treatment by procaine block of the stellate ganglion J A.M A *146*· 774 777, 1951
63 Vaernet, K Two cases of shoulder hand syndrome in meningioma affecting the premotor region Acta psychiat et. neurol. Scandiav *27*. 201-209, 1952.
64 Vaillan Court De, G · Shoulder hand syndrome. Union Med du Canada *83*. 25-29
65 Westhues, H Shoulder arm pain Med klin. *48*· 33-36, 1953
66. Woolf, D L. A case of shoulder-hand syndrome Ann Phys Med *1*: 266, 1953
67 Young, J H, and Pearson, A T The shoulder-hand syndrome. M. J. Australia *1* 776-780, 1952
68 Shoulder hand syndrome Heart Bull May June, 1956
69 Prevention of the shoulder-hand syndrome G. P. *12* 198 9, 1955

The Metabolic Origin of Uric Acid

by J. E. Seegmiller and L. Laster

BECAUSE THE MEDICAL LITERATURE suffers from no lack of articles concerne with uric acid and gout, the perpetrators of a new paper concerning eithe of these subjects must justify their addition to the metabolic pool of scientific writings Developments of recent years indicate that we may be at the beginning of an age of medical biochemistry in which the fine details of human physiology will be discovered and applied to the treatment of disease The field of purine metabolism, like many others, has shown the impact of intensive research in biochemistry, and during the past decade pathways of metabolism have been discovered which may be responsible for the synthesis of uric acid in the human body. In order that the clinician may keep pace with these rapid advances in the basic sciences and be prepared to reap the benefits that might come from this work, it seems warranted to review present concepts of the metabolic origin of uric acid.

The importance of uric acid in clinical medicine rests, at present, primarily on its relationship to gout, an hereditary disorder long known to be accompanied by an elevation of the serum urate level.[1] Hyperuricemia occurs also in many asymptomatic relatives of gouty patients, few of whom develop the disease. In the course of hematologic diseases, such as leukemia, polycythemia, myeloid metaplasia, multiple myeloma and hemolytic anemias, a hyperuricemia may appear. Some of the hyperuricemic individuals will then go on to develop episodes of acute arthritis indistinguishable from gout Such "secondary gout," as Gutman terms it,[2] may in time provide a clue to the relationship between the acute arthritis and the elevated serum urate level of gouty patients, which at the present time is not clear.

Uric acid, a member of the class of nitrogen-containing compounds known as purines, is a relatively insoluble substance which in birds and reptiles is the end product of nitrogen metabolism. In mammals, however, urea serves this purpose and relatively small amounts of uric acid are produced In most mammals the enzyme uricase degrades this uric acid to a soluble compound, allantoin, prior to excretion Because man and the higher apes lack uricase, they excrete uric acid Most of it appears in urine and small quantities are detectable in sweat, tears and feces. Recent studies[3] indicate that despite his lack of uricase, normal man can nevertheless break down as much as 18 per cent of his uric acid and excrete the nitrogen portion as urea and ammonia Uric acid can be broken down by enzyme systems

other than uricase in vitro,[4] but the particular enzymes involved in human uricolysis have not yet been identified.

Uric acid exists as the mono-alkali salt in body fluids. As determined with the usual colorimetric laboratory methods,[5] the normal serum value for men is between 2 and 6 mg per cent, and for reasons as yet undiscovered, it tends to be slightly lower in women. An improved enzymatic method[6] indicates that these colorimetric methods give values that are about 10 per cent lower than true serum urate levels Renal diseases in which the glomerular filtration rate is low produce elevations of serum urate with BUN and NPN elevations. Although other conditions may also be associated with hyperuricemia, it seems that the tendency for urate to deposit as chalky precipitates in the tissues is quite characteristic of gout and is seen only rarely in other disease states These tophi are primarily responsible for the chronic disability that may accompany gouty arthritis

The total amount of "miscible uric acid" in the body of normal man has been found by Stetten et al.[7] and Talbott et al.[8] to be around 1.2 Gm., as determined by the extent to which urate labeled with N^{15}, the heavy isotope of nitrogen, is diluted after intravenous injection In gouty subjects, values up to 30 times as great have been reported.[9] This exceeds by far the solubility of urates in body fluids and is evidence that a portion of the tophaceous deposits are in a dynamic equilibrium with the serum urate. The work of Stetten, Gutman, and associates[10] has shown that in some gouty patients an endogenous over production of urate may contribute to the hyperuricemia and therefore to the deposition of tophi. Because of the possible clinical *implications of this finding, it behooves the clinician to have a broad under*standing of the biosynthesis of uric acid.

A discussion of urate biosynthesis will be made clearer by an initial *definition of the chemical terminology involved* The nitrogen-containing purines and the related compounds, pyrimidines, occur inside cells as parts of complex molecules called nucleic acids. Nucleic acids are long chains made up of a repeating unit, the nucleotide, which is itself composed of three parts; a nitrogenous base which may be either a purine (adenine or guanine) or a pyrimidine, a five-carbon sugar (ribose or 2-deoxyribose) and a phosphate group attached to the sugar. Nucleotides not only comprise nucleic acids, but in themselves serve a variety of important functions in the cell The nucleotide adenine-ribose-phosphate-phosphate-phosphate, called adenosine triphosphate or ATP, by shuttling its two terminal "high energy" phosphate groups from one cellular biochemical system to another, acts as a *medium of* energy exchange The biochemically active forms of such vitamins as nicotinamide and riboflavin are also nucleotide compounds and are involved in cellular oxidation reactions.

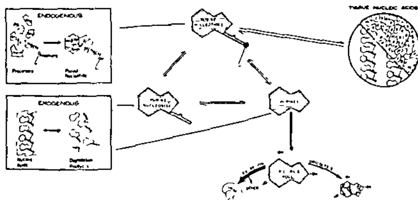


Fig 1 Uric acid production and disposition in man The sources of purine compounds contributing to uric acid production are shown

The nucleotides of nucleic acids are linked together by bonds running from the phosphate group of one to the ribose portion of another, to form long chains of polynucleotides If the sugar of the nucleotides is desoxyribose, the nucleic acid is desoxyribonucleic acid or DNA DNA comprises the main component of the chromosomal material of the cell nucleus and is believed to transmit inherited characteristics Nucleic acids containing ribose are termed ribonucleic acids, pentose nucleic aids, RNA, or PNA. Found mainly in the cytoplasm of the cell, RNA may well be involved in the biosynthesis of proteins and undergoes a much more active turnover than DNA

With the various terms of purine chemistry defined, we are now in a position to describe the main pathways of metabolism leading to the production of uric acid (fig 1). In the box labeled "Endogenous" we depict the intricate series of chemical reactions by which the body combines simple compounds to form a complete purine nucleotide, hypoxanthine-ribose-phosphate, also called inosinic acid. The origins of the atoms of this nucleotide are summarized in figure 2. Inosinic acid is converted to a variety of nucleotides, each having a different purine base. The adenine and guanine nucleotides serve to replace and replenish their counterparts in tissue nucleic acids As the tissue nucleic acids undergo their natural turnover, the adenine and guanine derivatives emerge for further metabolism

Nucleotides are degraded in step-wise fashion, first to nucleosides (purine-ribose) and then to free purines The free purines can enter a stream of enzymatic reactions leading to uric acid the excretion product. The nucleoproteins of ingested foodstuffs, made up of nucleic acids attached to proteins, can also contribute to uric acid production (see box labeled "Exo-

FIG 2 The metabolic origin of the various atoms of a purine nucleotide (hypoxanthine ribose-phosphate) and its schematic representation (see Fig 1)

genous," fig 1) Free nucleic acids, released in the stomach by proteolytic enzymes, are degraded in the small intestine, probably to the nucleoside stage, and then absorbed. The purines of these foodstuffs, like their endogenously-produced analogues, can then be incorporated into tissue nucleic acids[11, 12] or degraded to uric acid.[13]

In summary, it should be noted that uric acid can be derived from nucleotides by direct degradation before and/or after incorporation into tissue nucleic acids Moreover, nucleotides can be supplied in foodstuffs from exogenous sources, or they can be made by the body. The discovery during the past ten years of the details of this endogenous production of uric acid is a major achievement of biochemists and will now be discussed.

In the early 1940's the origin of the purine ring was not fully understood. It had been known[14] that glutamine, among other amino acids, could increase purine production by slices of animal tissue in vitro. The subsequent

developments in this field are an example of the manner in which the use of isotopically labeled compounds has served to clarify long standing problems. In 1943, Barnes and Schoenheimer,[15] pioneers in the use of heavy isotopes, fed ammonium citrate labeled with N^{15}, the heavy isotope of nitrogen, to rats and pigeons. They found significant amounts of isotope in tissue purines and pyrimidines and in the degradation products of purines isolated from the excreta. With this direct evidence that the purine ring was synthesized in the body from smaller building units, Buchanan and his co-workers went on in a series of now classical studies,[16,17] to identify the sources of the various atoms that make up a purine ring (fig 2). Using glycine labeled with heavy carbon, C^{13}, in the carboxyl position, these men demonstrated that glycine was incorporated into uric acid in the pigeon. While this work was in progress, Shemin and Rittenberg were studying the lifespan of human red blood cells by feeding N^{15}-glycine. When they learned of Buchanan's work, they isolated uric acid from the urine of a patient used for the red blood cell survival studies and found that isotopic nitrogen had appeared in the urinary uric acid.[18] This was the first direct demonstration that man too could synthesize uric acid from smaller building blocks although earlier work[19] had shown that there is no dietary requirement for purines in man. Information that was to provide another wedge into the problem of purine biosynthesis came from work that appeared totally unrelated to the field of purine metabolism.

In 1942 Fox discovered that cultures of E. Coli, grown under conditions of sulfonamide bacteriostasis, accumulate an amine which gives the same color reactions as do sulfa drugs, but is not in itself a sulfonamide.[20] In 1945 Stetten and Fox isolated this compound for the first time in pure form[21] and eventually, in 1947, Shive and co-workers demonstrated it to be 4-amino-5-imidazolecarboxamide (AIC), a compound that is one carbon atom short of being a purine.[22] They proposed that sulfonamides interfere with the enzymatic reactions involved in transfer of single carbon units. A folic acid derivative has since been shown to mediate this one-carbon unit transfer in biological systems. The sulfonamides thus act to produce a deficiency of folic acid thereby interfering with the conversion of AIC or a derivative into an intact purine ring.

This conclusion was confirmed when Miller, Gurin and Wilson demonstrated the incorporation of AIC-C^{14} into purines and purine breakdown products in the rat.[23] Soon afterwards, Schulman, Buchanan and Miller showed that homogenates of pigeon livers could incorporate labeled AIC into the purine ring at rates comparable to those detected when labeled glycine and formate were used as precursors.[24] Subsequent studies in several laboratories revealed that the true intermediate in purine metabolism is not the

free base AIC, but its ribotide, AIC-ribose-phosphate [25, 26] Evidence that pathways of purine synthesis in the human may be similar to those discovered in animals was obtained in experiments by Stetten, Seegmiller and Laster which showed that AIC-C^{13} is incorporated into uric acid by the normal human.[27]

In view of these similarities between animal and human purine biosyn-

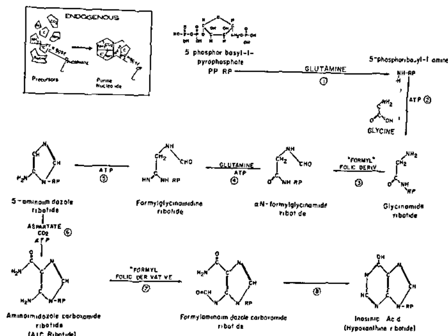


FIG 3 The sequence of enzymatic reactions involved in purine biosynthesis

thesis, and because, with only minor exceptions, overall pathways of metabolism elucidated in one animal species have been found to occur generally in other species, we shall describe in detail the current concept of metabolic pathways for the synthesis of purines in lower animals from simpler compounds (fig 3) [28, 29] This synthesis starts with the active form of the sugar, ribose, on which there is a single phosphate unit attached to one end of the molecule and a double phosphate unit to the other. This active ribose, PP-RP, then receives a nitrogen atom from the amide portion of the amino acid glutamine (reaction 1). In reaction 2, three atoms are added in a single unit arising from the intact molecule glycine, the simplest amino acid of the body This is followed (reaction 3) by the first of two one-carbon additions. These one-carbon, active "formyl," units are donated by tetrahydroformyl-folic acid, the biologically active form of folic acid, which functions to transfer formyl groups in a variety of biochemical systems. An additional nitrogen atom is

then received from the amide group of glutamine (reaction 4), and ring closure (reaction 5) forms a five-membered cyclic compound This imidazole ring is one of the two heterocyclic rings comprising the purine structure The subsequent additions (reaction 6) of a carbon atom from CO_2 and a nitrogen atom from aspartic acid, an amino acid, produce the now familiar compound, AIC ribotide (5-amino-4-imidazolecarboxamide ribotide), the discovery of which we have already discussed The addition (reaction 7) of a second "formyl" group from tetrahydroformyl-folic acid, and ring closure (reaction 8), complete the biosynthesis of the purine ring by producing hypoxanthine-ribose-phosphate, inosinic acid This nucleotide stands at a common meeting point for several pathways of nucleotide interconversions (fig. 4)

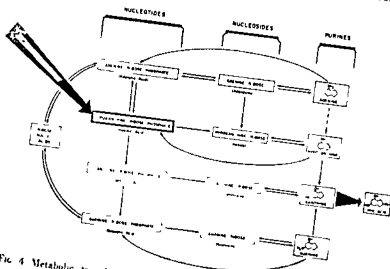


FIG. 4 Metabolic transformations of purine compounds and pathways for their conversion to uric acid

One set of reactions involv[illegible]
the nucleotides used for the [illegible] ormatio[illegible]
while another pat[illegible] ithin
first to the nuc[illegible] nucl
The enzyme x[illegible] oxa
acts on the [illegible] and
involves the c[illegible] inic
phosphate) w as[illegible] -ri
can r[illegible]

guanylic acid (guanine-ribose-phosphate). Studies have shown that inosinic acid can also be converted to adenylic acid (adenine-ribose-phosphate).[31, 32] The three nucleotides, adenylic, xanthylic and guanylic acids, all undergo degradative conversions to the free purines, adenine, xanthine and guanine, and guanine is further converted to xanthine which is oxidized by xanthine oxidase to form uric acid. Evidence that adenine may undergo a similar reaction in mammalian tissues is not conclusive. Interconversions can occur before the free purine stage and these are shown in the diagram.

Adenylic and guanylic acids can each be transformed into their triphosphate derivatives (purine-ribose-phosphate-phosphate-phosphate), ATP and GTP. These compounds function in a variety of reactions involving energy transfer The diphosphate derivatives of adenylic and guanylic acid are converted to the polynucleotide chains that go to form nucleic acids and thus provide the means by which purines are incorporated into these vital constituents of cells.[33]

In summary, studies using animal tissues have demonstrated the occurrence of several different chemical routes for the biosynthesis of uric acid We have described a sequence of enzymatically catalyzed reactions by which small molecules combine to form the nucleotide, inosinic acid. This compound can then be converted to the purine derivatives needed for the production of nucleic acids, or it can undergo degradative reactions, as can its derivatives, and ultimately meet its fate as uric acid. Additional interconversions and back reactions may yet be discovered since purine metabolism continues to be an active area of research The relative importance of these pathways in human biochemical processes also remains to be studied. The correlation of such information with diseases in which abberations of purine metabolism occur should prove a fertile field for clinical investigation

A start in this direction has been made in the investigation of the metabolic defect in gouty patients. Stetten et al. have demonstrated that in some gouty patients glycine-N^{15} is incorporated into urinary uric acid more promptly and in greater quantity than in the normal.[10] Since then Wyngaarden has performed similar studies using glycine-1-C^{14} and reports[10a] his defect to be present in all the six gouty patients and one patient with essential hyperuricemia that he studied. The precise pathway along which his accelerated endogenous synthesis of uric acid occurs, remains to be determined. It is quite possible that this pathway may be among those shown in figures 3 and 4 and the information summarized in these charts can reasonably serve as a guide for further investigation. A study of the pattern of incorporation of some of the purine precursors shown in these charts into uric acid in the gouty subjects may very well serve to delineate the metabolic defect responsible for this excessive production of uric acid. The nature of the regulatory mechanism governing endogenous purine pro-

duction is not well understood. Stetten and co-workers have demonstrated that a high protein diet results in an increased urate production from glycine-N^{15} as compared to a low protein diet.[34] This has obvious implications for the clinical management of certain gouty patients.

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References

1. *Garrod, A B* The Nature and Treatment of Gout and Rheumatic Gout London, Walton and Maberly, 1859
2. Gutman, A B: Primary and secondary gout Ann. Int. Med 39: 1062, 1953
3 Wyngaarden, J. B, and Stetten, DeW Jr Uricolysis in normal man. J. Biol Chem. *203: 9, 1953.*
4. Cannelakis, E S, Tuttle, A L., and Cohen, P. P.: A comparative study of the end products of uric acid oxidation by peroxidases J. Biol Chem 213: 397, 1955
5 Forsham, P. H, Thorn, G W, Prunty, F T. G, and Hills, A. G.: *Clinical studies* with pituitary adrenocorticotropin. J Clin Endocrinol 8: 15, 1948
6 Praetorius, E An enzymatic method for the determination of uric acid by ultraviolet spectrophotometry, Scandinav J Clin & Lab Invest 1: 222, 1949
7 Benedict, J. D, Forsham, P H, and Stetten, DeW Jr: The metabolism of uric acid in the normal and gouty human studied with the aid of isotopic uric acid J Biol Chem *181*: 183, 1949
8. Bishop, C, Garner, W, and Talbott, *J H. The* pool size, turnover rate, and rapidity of equilibration of injected isotopic uric acid in normal and pathologic subjects *J Clin. Invest 30: 879, 1951*
9 Benedict, J D, Forsham, P H, and Stetten, DeW. Jr: *The effect of salicylates* and adrenocorticotropic hormone upon the miscible pool of uric acid in gout. J Clin Invest 29: 1104, 1950
10. Benedict, J. D, Yu, T F, Bien, E J, Gutman, A. B, and Stetten, DeW. Jr: A further study of the utilization of dietary glycine nitrogen for uric acid synthesis in gout J Clin Invest 32: 775, 1953.
10a Wyngaarden, J Overproduction of uric acid as the cause of hyperuricemia in primary gout, abstract, meeting of the American *Society for Clinical Investigation*, May, 1957, p 74
11 Hamilton, L Utilization of purines for nucleic acid synthesis in man Nature *172* 457, 1953
12 Lowy, B A, Davoll, J, and Brown, G B The utilization of purine nucleosides for nucleic acid synthesis in the rat J Biol Chem *197*: 591, 1952
13 Wilson, D, Beyer, A., Bishop, C, and Talbott, J H: Urinary uric acid excretion after the ingestion of isotopic yeast nucleic acid in the normal and gouty human J Biol Chem *209*: 227, 1954
14 Öström, A, Öström, M, and Krebs, H A: The formation of hypoxanthine in pigeon *liver Biochem* J 33 990, 1939
15. Barnes, F. W, and Shoenheimer, R On the biological synthesis of purines and pyrimidines J Biol Chem *151*. 123, 1943.
16 Sonne, J C., Buchanan, J M, and Delluva, A M: Biological precursors of uric acid. II The role of lactate, glycine, and carbon dioxide as precursors of the carbon chain and nitrogen atom 7 of uric acid J Biol Chem *173* 81, 1948
17 Sonne, J C, Lin, I, and Buchanan, J M: Biosynthesis of the purines IX Precursors of the nitrogen *atoms of the purine ring J Biol. Chem 220*: 369, 1956.
18. Shemin, D, and Rittenberg, D: On the utilization of glycine for uric acid synthesis in man J Biol Chem *167*: 875, 1947
19 Kollman, G. Über Harnsäuresynthese in Menschlichen Organismus. Biochem Z. *123* 235, 1921

20 Fox, C. L., Jr. Production of a diazotizable substance by *Escherichia coli* during sulfonamide bacteriostasis Proc Soc Exper Biol & Med *51* 102, 1942
21 Stetten, M R and Fox, C. L.: An amine formed by bacteria during sulfonamide bacteriostasis J Biol Chem *161* 333, 1945
22 Shive, W., Ackermann, W. W., Gordon, M., Getzendaner, M E., and Eakin, R. E. 5(4)-amino-4(5) imidazolecarboxamide, a precursor of purines J Am Chem Soc *69*, 725, 1947.
23 Miller, C. S., Gurin, S., and Wilson, D. W: C^{14} Labeled 4(5) amino 5(4)-imidazolecarboxamide in the biosynthesis of purines Science *112* 654, 1950
24 Buchanan, J. M., and Schulman, M P Biosynthesis of the purines III Reactions of formate J. Biol Chem *202* 241, 1953
25 Schulman, M P, and Buchanan, J M Biosynthesis of the purines. II Metabolism of 4-amino 5 imidazolecarboxamide in pigeon liver J Biol. Chem. *196*: 513, 1952.
26 Greenberg, R G. *De novo* synthesis of hypoxanthine via inosine-5 phosphate and inosine J Biol Chem *190*: 611, 1951
27 Seegmiller, J E, Laster, L., and Stetten, DeW Jr Incorporation of 4 amino-5-imidazolecarboxamide-4 C^{13} into uric acid in the normal human J Biol Chem *216* 653, 1955
28 Brown, G B. Chemical pathways of nucleic acid biosynthesis Federation Proc *15* 823, 1956
29 Goldthwait, D A, Peabody, R A., and Greenberg, R A The occurrence of glycinamide ribotide and its formyl derivative. J. Biol Chem *221* 555, 1956
30 Magasanik, B., Moyed, H. S., and Karibian, D Interconversions of purines in the biosynthesis of nucleic acid adenine and guanine and of histidine J Am Chem Soc *78*. 1510, 1956
31 Abrams, R., and Bentley, M Transformation of inosinic acid to adenylic and guanylic acid in a soluble enzyme system J. Am Chem Soc *77* 4179, 1955
32 Lieberman, I Enzymatic synthesis of adenosine 5 phosphate from inosine 5 phosphate J Biol Chem *223* 327, 1956
33 Grunberg-Manago, M., and Ochoa, S. Enzymatic synthesis and breakdown of polynucleotides, polynucleotide phosphorylase J Am Chem Soc *77* 3165, 1955
34 Bien, E. J., Yu, T F., Benedict, J D, Gutman, A. B., and Stetten, DeW Jr The relation of dietary nitrogen consumption to the rate of uric acid synthesis in normal and gouty man J Clin Invest *32* 778, 1953
35 Burchenal, J H., and Krakoff, I H Newer agents in the treatment of leukemia Arch Int Med 98 567, 1956

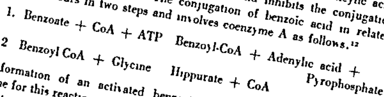
The Sustained Administration of Benemid (Probenecid) in the Treatment of Gouty Arthritis

by John H. Talbott

THE TREATMENT OF GOUT *and gouty arthritis embraces the management of* acute articular symptoms, the prevention of recurring acute attacks and the resorption of urate deposits. In the alleviation of the acute articular episode the only specific antirheumatic agent recognized in the pharmacopeia, colchicine, has been available for centuries, either as the impure or the refined product. Although of value in prophylaxis as an antiarthritic agent, colchicine has no demonstrable effect upon the intermediary metabolism of uric acid or the exchange of this substance by the kidney. The search for a compound capable of restoring the dysfunction in the intermediary metabolism of uric acid in gouty patients has so far proved fruitless More rewarding, however, have been the investigations in the field of uricosuric agents. While the uricosuric action of salicylates has been recognized for almost a century, that of cincophen has been known for a somewhat shorter period of time. Several years ago the uricosuric action of hyperglycemia, intravenous Diodrast and mercurial diuretics was revealed.[14] This, in brief, relates the status of uricosuric agents until recently.

Historically, the rheumatologist has lacked an effective uricosuric agent that possesses low toxicity and is amenable to oral administration in small enough quantities to be tolerated, even though it were necessary to administer it daily year after year. Shortly after the second world war, a renewed search was begun for the desired pharmacologic preparation. Encouraged by favorable responses in earlier studies, we centered our investigations upon various preparations with iodine components similar to Diodrast The results were disappointing. At the same time, industrial biochemists were investigating a number of preparations designed to inhibit the excretion of penicillin by the renal tubules in order to achieve a higher blood level without altering the quantity of penicillin administered. Of the several substances investigated, which included the diisopropyl and diisopropanol analogues of probenecid, dibutylsulfamyl, diisobutylsulfamyl, and disecondary butylsulfamylbenzoic acid, caronamide was found to be an effective inhibitor of penicillin excretion by the renal tubules. Interestingly enough, the reabsorption of urates from glomerular filtrate was inhibited simultaneously with the inhibition of excretion of penicillin. In order to produce effective uricosuria, it was necessary to administer excessively large doses of caronamide (18-24 Gm.

o. d.), an impractical quantity for long-term management.[14] Because of lo toxicity of caronamide, however, the search continued for a related com pound that would be effective in considerably smaller quantities. As a result, probenecid (p-(di-n-propylsulfamyl)-benzoic acid) was selected, and in 1950 clinical trials were started. Probenecid (Benemid) alters not only the renal exchange of penicillin and uric acid but also that of p-aminosalicylic acid, p-aminopuric acid and phenolsulfonphthalein and inhibits the conjugation of glycine and benzoic acid.[2] The conjugation of benzoic acid in related compounds occurs in two steps and involves coenzyme A as follows.[12]



The formation of an activated benzoate, namely, benzoyl-CoA and the enzyme for this reaction, is provided by ATP (adenine triphosphate). Action 2 is a transfer of the benzoyl group from CoA to glycine.[6] Benemid has been shown to compete effectively with benzoate in the activation reaction but has no effect upon the subsequent transfer to glycine. To explain this phenomenon, it has been postulated that the intermediate compound in the renal transport of penicillin and related substances is the CoA complex. By forming a complex with CoA that is less dissociable than that of penicillin, Benemid interferes with the transport. The cellular mechanisms for uric acid transport as well as the inhibition of the mechanisms by Benemid remain completely unknown, even though the operation described above is applicable to penicillin. Benemid neither affects the urinary excretion of any known important endogenous substance other than uric acid nor affects in any manner the other electrolytes handled by the kidney.[11] A modest diuresis with an increased urinary excretion of sodium and chloride has been observed in nongouty edematous persons.[5] Benemid neither enhances nor negates the antirheumatic action of colchicine when administered simultaneously.

The exchange of urates by the kidney in the normal control, is similar to that of the patient with gout prior to the development, when this occurs, of extensive functional impairment in this organ. It is generally accepted that urates appear in glomerular filtrate in essentially the same concentration as they exist in a protein free filtrate of plasma. Approximately 90 per cent of the urates in glomerular filtrate are absorbed by the renal tubules while the remaining 10 per cent is allowed to pass into the bladder and be excreted. Under the action of Benemid, glomerular filtration is unaltered. The site of action is believed to be the tubular cells. Because of the partial blocking reabsorption only 80 per cent of urates in glomerular filtrate re-enter the renal cells instead of 90 per cent. The remaining 20 per cent is excreted. The increase in the excretion of urates in glomerular filtrate, from 10 to 20 per

two years of continued ingestion of Benemid (fig 1) This function has not been measured in this laboratory after a longer maintenance period but I have reason to believe that if the metabolic pool remains depressed under the uricosuric action of Benemid after two years of therapy, it very likely will remain depressed as long as the increased urinary excretion and the decrease in the serum concentration are observed. The return toward normal of serum urate is a function of the concentration of Benemid in the serum, over the range 0 to 5 mg /100 ml of Benemid (fig 2) Thereafter, higher concentrations of Benemid exert a negligible effect upon the concentration of serum urate

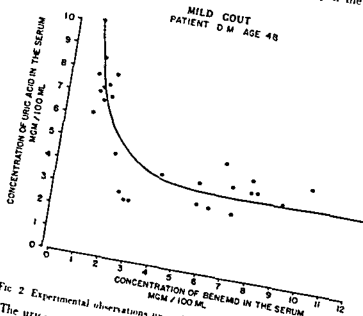


FIG 2 Experimental observations upon the concentration of uric acid and Benemid

The uricosuric action of Benemid may be nullified, totally or partially, by the simultaneous administration of salicylates. Pascale and associates[a] observed that 5 Gm. of acetylsalicylic acid suppressed completely the uricosuric action of 2 0 Gm. of Benemid Because of this antagonistic action, salicylates should not be prescribed during the Benemid regimen. Also Benemid increases to some degree the level of free and conjugated sulfonamide in the blood Therefore, if sulfonamides are given to a patient receiving Benemid, the course of the former should be a relatively short one.

When Benemid first became available for clinical trial, toxicity studies were derived largely from non gouty subjects. The review of the records of

cent, results in a two-fold increase in urinary excretion of this substance Values of this magnitude are not maintained in long-term therapy, although an increased urinary excretion of uric acid of the order of magnitude of 30 or 40 per cent may be expected with maintenance doses of Benemid not greater than 1 Gm. per day

The clinical trials with Benemid, begun in 1950, continue to elicit our praise for this drug and no events have influenced us to dampen our enthusiasm. Benemid, rapidly and effectively absorbed from the gastrointestinal tract when taken orally, is carried in the blood stream partially bound by plasma protein. The unbound portion gains access to the glomerular filtrate but is largely resorbed by the renal tubules. The blocking action of Benemid may be demonstrated within a few hours after beginning ingestion A decrease in concentration of uric acid in the serum follows immediately the increased excretion of uric acid in the urine. Occasionally the depression during the first few days after beginning Benemid may be greater than that observed subsequently, but at no time is it abolished and with but few exceptions, the alteration of both functions may be demonstrated as long as the drug is ingested.

A decrease in the size of the metabolic pool has been observed after

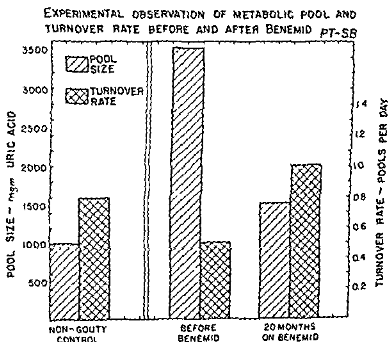


FIG. 1. Metabolic pool size and turnover rate as a function of Benemid intake.

been operated upon for a large urate calculus that could not be handled by medical means. During the preceding seven-year period, with a somewhat smaller number of patients in the series, surgical removal of a urate stone was necessary also in two instances. It should be appreciated that the incidence of renal stones in patients with gout is approximately 15 per cent We have recently calculated the incidence among our patients on Benemid and find that the percentage since 1950 agrees precisely with that recorded by Kittredge and Downs[8] In order to obtain reliable control data regarding incidence of renal stones, it is necessary to collect statistics over a period of years rather than for shorter periods of time It should be noted that in some patients a urate calculus may precede the onset of acute articular gout by a number of years

The presence of mild renal dysfunction is not a contraindication to the administration of Benemid. There are a few patients in our series with an elevated blood urea nitrogen whose gout appears to respond as effectively to Benemid as do the much larger number of patients without demonstrable renal insufficiency. Several patients with a significant elevation of the blood urea nitrogen have been ingesting Benemid regularly for several years without experiencing untoward effects from this agent Since a significant percentage of those afflicted with gout show some evidence of renal dysfunction (more than 25 per cent in our series), such patients might be deprived of possible benefit if Benemid were found to be harmful On the other hand, Phillips has noted improvement in renal function in one patient after three years of Benemid[10] Our observations have been reassuring but not so spectacular.

Precipitation of acute attacks of gout following the institution of Benemid appeared to us to pose as real a threat as did the development of renal stones in the early experimental period. This fear has not been substantiated by clinical experience Initially, it was our practice to caution patients concerning the possibility of an acute attack developing after embarking upon the Benemid regimen Statistical evidence has revealed that the incidence of acute exacerbations during the first few months after beginning Benemid with full doses of the drug is slightly less than in the pre-Benemid period. Boger and Smith[3] have tabulated the incidence of acute exacerbations before and after beginning Benemid in patients receiving one of three quantities of Benemid daily In each of the categories the incidence of acute attacks was reduced significantly Since the incidence of recurrence poses a threat to the patient, it may be desirable, in selected instances, to begin with small doses of Benemid and increase to maintenance quantities over a period of a few weeks. In the light of statements in the literature regarding possible exacerbations, it may be desirable to follow such a schedule when either the physician or patient feels apprehensive

The value of Benemid rests exclusively with its use as a prophylactic

more than 2000 non-gouty patients, who received probenecid *in doses varying between 0.5 and 2.0 Gm. per day, revealed* a toxicity of approximately 8 per cent.[4] Anorexia and nausea were the most frequently observed complaints. This distress was relieved usually by decreasing the dosage. Another effective means of eliminating anorexia and nausea at the higher dose levels *has been to insist upon the ingestion of Benemid at mealtime.* Bone marrow depression or liver damage has not been observed in this laboratory or in others.[7] True drug sensitivity to Benemid has been observed in a few patients with gout. There were three patients in our series who developed a *skin rash In the case of one patient, there* was some *question whether the* skin rash was related to Benemid intake, or to some other event. Since the patient was exposed to droplets of acid at his job, this was considered as a possible causative agent. Although the rash was observed more than five *years ago; the patient meanwhile has continued on Benemid daily without* a recurrence. Another patient developed pruritis after a fortnight of Benemid, 1 Gm. daily. Cessation of Benemid and the administration of an antihistaminic proved only partially successful in the management of the side effect *Complete subsidence of symptoms did not occur for more* than two weeks Ingestion of Benemid was resumed later together with an anti-histaminic Eventually, the anti-histaminic was eliminated and Benemid ingestion continued without a recurrence of the pruritis. One severe anaphylactic reaction from Benemid in a physician has been reported in the literature.[1] Infinitesimally small doses were administered subsequently in order to desensitize the patient Eventually this was accomplished and the desired pharmacologic action of Benemid achieved. Reynolds and associates have reported recently[11] the postmortem finding of massive necrosis of the liver that was attributed to hypersensitivity to Benemid. A survey of the literature revealed no similar observation, nor do I have any information of a similar case

In my judgment, the only significant side effect from the administration of Benemid is the passage of uric acid gravel or symptoms associated with a urate calculus. Since an increased excretion of uric acid from the body is the desired pharmacologic effect, it is reasonable to expect that the tendency to the development of stones or gravel in the genito-urinary tract is potentially a serious clinical problem. Each patient started on *Benemid* in our series, during the preliminary period of clinical investigation, was cautioned regarding the possibility of complications from renal calculi. At this time, however, we are firmly convinced that Benemid has not altered the incidence of renal stones. Renal colic has appeared *from time to time*, and a limited few patients have been hospitalized for observation following the development of symptoms suggestive of renal colic. Occasionally patients have been observed who have had mild ureteral pain caused by passage of *urate gravel* Symptoms *may persist for several days.* Two patients have

at a given dose level within a few days after embarking upon the regimen Some escape from the maximum uricosuric effect may be apparent from time to time, and the serum level especially tends to be a little higher on maintenance doses month by month than during the first few days after beginning Benemid. This fact is illustrated in patient J.B., who was followed for three years before Benemid became available This patient has been on Benemid now for more than six years (fig. 4). During the period on colchicine alone, the concentration of uric acid in the serum varied between 7.5 and 10 5 mg Immediately prior to the addition of Benemid to the prophylactic regimen, the concentration of uric acid in the serum was 7.8 mg The patient was placed upon 2.0 Gm. of Benemid daily and the concentration of uric acid in the serum was reduced to 4 0 mg. A maximum depression to 3 7 mg. was noted During the sixth year of Benemid intake the concentration of uric acid in the serum was 5 8 mg. This represents a significant decrease from the three-year average prior to beginning Benemid

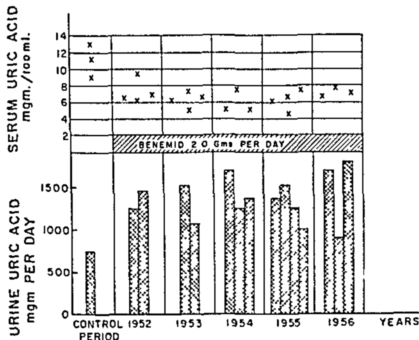


FIG. 3 Experimental observations upon the concentration of uric acid in the serum and urine as a function of Benemid intake

The average decrease in concentration of the serum with a 1 or 2 Gm dose of Benemid daily ranges from 20 to 40 per cent (fig. 5) The effect is

agent in the intercritical period. Benemid is endowed with no immediate anti-inflammatory action. Any effect in relation to the acute attack concerns its prevention, not its immediate management. Since the greater portion of the time of any patient with gout should be the period between the attacks, this places Benemid in the high priority category. When the prophylactic regimen is followed, the results are impressive, and most patients are restored to normal activity.

Although this discussion is concerned primarily with Benemid, it should be noted that the prophylactic regimen embodies a combination of colchicine and Benemid. Colchicine, in prophylactic doses (0.5-1.0 mg daily), is believed to exert its action primarily in preventing or aborting acute articular episodes. The action of Benemid is exclusively upon the renal exchanges of urates. When the two drugs are taken regularly in combination, prophylaxis becomes factual and effective. We have not used Benemid alone in the intercritical period except in a few instances and then only after the combined colchicine and Benemid regimen has been maintained for several years. There have been isolated instances brought to our attention, however, of patients with gout who have received Benemid without colchicine. The clinical results have been disappointing. The uricosuric action of Benemid has been operating, but the antirheumatic action of colchicine has been lacking. Undoubtedly, the incidence of acute attacks would have been influenced eventually if Benemid had been ingested for one or more years, but this approach to management seems to be wrong, for it fails to take full advantage of the combined colchicine-Benemid regimen.

At the beginning of the experimental study of Benemid, several patients were placed upon doses as high as 3 Gm. a day. This resulted in an excellent uricosuric action at the expense of gastrointestinal symptoms. Some time later, the maximum dose of 2 Gm. per day was decided upon for those severely afflicted. Those moderately or mildly afflicted were prescribed 1 Gm. per day. We proceeded originally upon the assumption that the larger the quantity of Benemid ingested, the more effective the uricosuric action and the greater the inhibition of the tendency to urate precipitation in bony and soft tissues. While this assumption remains theoretically, clinical experience has been thoroughly satisfactory with submaximal doses. The beneficial results associated with the combined colchicine-Benemid regimen are impressive. They surpass those obtained when colchicine was the only prophylactic drug available and leave no doubt regarding the complementary value of Benemid.

There are two actions that may be attributed directly to Benemid and two actions that Benemid shares with colchicine. An increased excretion of uric acid in the urine and a decreased concentration in the serum is the biochemical desideratum of Benemid (fig. 3). A maximum change occurs

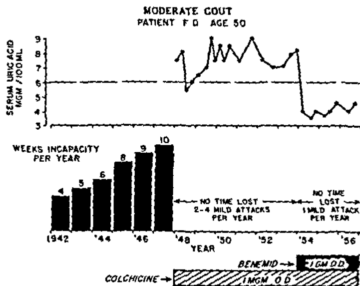


Fig. 5. Days of incapacity before and after the colchicine-Benemid regimen

loss of uric acid in the urine requires additional fluid if uricosuria is to be effective. Nor is there any prohibition to a reasonable intake of alcoholic beverages.

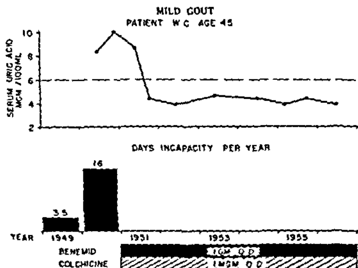


Fig. 6. Days of incapacity before and after the colchicine-Benemid regimen

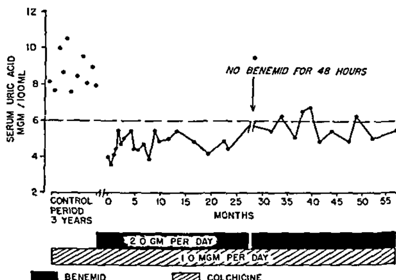


Fig. 4 The effect of Benemid intake upon the concentration of uric acid in the serum (Moderate gout. Patient J B Age 42)

slightly less when the dose of Benemid is smaller. Not more than 10 per cent of the patients in our series who take 1 Gm. or more of Benemid have failed to show a significant decrease in the concentration of uric acid in the serum. We do not know why the occasional patient fails to respond. It cannot be attributed to demonstrable renal dysfunction. Even the patients who have not responded with a statistically significant decrease in the concentration of uric acid in the serum have shown a clinical response, nevertheless This observation leads us to believe that Benemid is accomplishing some good even though the benefit cannot be confirmed in the biochemical laboratory The ultimate level on Benemid averages from 6 to 8 mg./100 ml if the level of uric acid in the serum is in the high gouty range, i e., from 8 to 12 mg./100 ml. If the uric acid disturbance is milder and the serum urate concentration lower, the uricosuric action of Benemid reduces the level to the normal range, i e., from 4 to 6 mg (fig. 6).

It should be emphasized that the general measures recommended for the management of gout are not difficult to carry out and do not embarrass the patient at home, at work or at play. The patient is encouraged to consume a balanced diet. Only those foodstuffs high in purine substances, such as liver, kidneys, sweetbreads and anchovies are prohibited. We have never recommended rigid protein restriction, and there appears to be even less reason for such restriction at the present time since Benemid is available. It is important to insist upon a liberal fluid intake because the increased

accumulation of Benemid by the body within the dose range as outlined. The effect is relatively transient and shortly after the ingestion of Benemid ceases, a prompt return of the serum urate level to the pre-Benemid value occurs. This escape does not indicate a nullification of the desirable action of Benemid but rather underlines the chronic nature of the disturbance



FIG. 8. Roentgenogram of the foot of the same patient illustrated in figure 7. This roentgenogram was taken two years later, in 1956. A significant decrease in the size of the osseous tophus in the fused portion is apparent.

and allows the reaccumulation of urates in the tissues to begin anew. Thus, the patient, moderately or severely afflicted with gout, probably should be on Benemid for longer periods of time. The patient mildly afflicted may follow a more liberal course.

The severity of the malady bears no relation to the effectiveness of the uricosuric action of Benemid. *Patients mildly afflicted, as well as those with* chronic tophaceous gout, experience a reduction in the incidence of acute attacks together with a response chemically, insofar as the partial or complete restoration of the abnormalities in the blood are measured. There is no



Fig. 7. Roentgenogram of a 49-year-old male with a long history of intermittent attacks of acute gouty arthritis. This roentgenogram was obtained in 1954. Extensive destruction of the joint space with fusion from gouty arthritis is apparent.

arthritis for 18 years is reproduced in figure 7. Extensive structural changes are apparent in the first toe. The patient was placed upon 2 Gm of Benemid daily. Three years later, the x-rays showed recalcification which undoubtedly



Fig. 10 Roentgenogram of the foot described in figure 8. This roentgenogram was taken in 1951 Degenerative changes are apparent with marked destruction of the metatarsal phalangeal joint of the 5th toe

Another specific effect of Benemid is the decrease in the size of subcutaneous tophi and recalcification of areas of decreased density in the bone. Two series of x-rays illustrate these changes. The roentgenogram of the foot of a 49-year-old male who had intermittent attacks of acute gouty

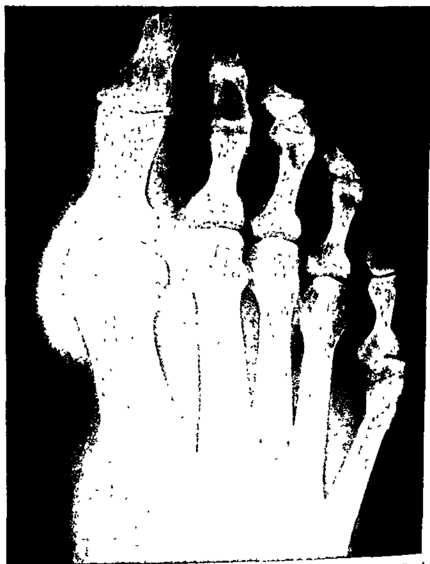


FIG 9 Roentgenogram of the right foot of a 54 year-old male who had suffered intermittent attacks of acute gouty arthritis for more than 30 years. This roentgenogram was taken in 1949 and shows the destructive lesions in the first and fifth toes.

a 2 Gm of Benemid in 1951 (fig 10). Two years later there was questionable improvement but also evidence of progression of the osseous tophi in selected areas (fig. 11). After the patient had been on Benemid for four years, he showed definite evidence of regression (fig. 12).



FIG. 12 Roentgenogram of the foot of the patient described in figures 8, 9 and 10. This roentgenogram was taken in 1955. Progressive healing of the destructive lesions is apparent.

was associated with partial replacement of urates by calcium salts (fig. 8). Another series of x-rays are illustrated in figures 9 through 12. These were observed in a 54-year-old male who had suffered intermittent attacks of acute gouty arthritis for more than 30 years (fig 9). The patient was placed upon



Fig 11 Roentgenogram of the foot described in figures 8 and 9 This roentgenogram was taken in 1953 The patient had been on Benemid for two years The destructive lesions in the 5th toe showed evidence of recalcification.

resulted because of the failure to take Benemid. The second patient, a physician, 80 years of age when first seen, is a sufferer from mild gout. He is now 88 years of age and has suffered no attacks in recent years; meanwhile he ingests colchicine periodically. When gastrointestinal irritability developed with doses of 2 Gm. of Benemid daily, it was discontinued. The third patient, who abandoned Benemid without our recommendation, started it and stopped it on two occasions because he felt it was responsible for substernal distress. Eventually he suffered severely from recurring attacks of acute arthritis and was persuaded to resume Benemid together with colchicine. He has suffered no further attacks of acute gout since the combined regimen has been accepted.

Neither an active peptic ulcer nor colitis appear to be strong contraindications of Benemid ingestion. We are following one patient with an active duodenal ulcer, demonstrated by x-ray intermittently, who tolerates colchicine, 1 mg. a day and Benemid 2 Gm. a day, as long as anti-ulcer recommendations are respected. There are three patients in our series who have "colitis." Minimal doses only of colchicine and regular doses of Benemid are tolerated well. Roentgenographic evidence of ulcerative colitis is present in one of the patients; the others complain of loose stools periodically.

We are firmly convinced that the combination of colchicine and Benemid provides the most effective treatment currently available for gout and the most effective means of attacking the outward manifestations of the disturbance of uric acid metabolism available at this time. Patients mildly or moderately afflicted are permitted to lead normal lives in every major respect. Those with chronic deforming gouty arthritis may be handicapped to a limited degree but are not incapacitated. We have several patients in our series, either forced to retire prematurely or to pursue part time jobs only, who have resumed a full-time gainful occupation following the combined therapy. Not a single patient in our series has become permanently handicapped or crippled while on the regimen, not a single patient has been forced to restrict further his gainful activities. Two patients have died during the past six years of causes directly related to gout, in each instance, because of longstanding severe renal insufficiency. Other causes of death during the past six years have included a dissecting abdominal aneurysm in a 56-year-old male, a third myocardial infarction in a 73-year-old male and carcinoma of the colon in a 76-year-old male.

The optimum length of time that a patient should be on Benemid daily has not been determined. It is our belief at this time that patients severely afflicted should continue on Benemid indefinitely. Patients moderately afflicted probably may revert to smaller doses with safety after Benemid has been taken regularly for two or more years, meanwhile maintaining some colchicine daily as anti-articular prophylaxis. Persons mildly afflicted have

There are no illustrations of regression of subcutaneous tophi. If large subcutaneous tophi are observed, it is our practice to remove them surgically rather than to wait for Benemid to reduce them gradually The cosmetic effect is achieved shortly after surgery, and the possible added load upon the kidneys in excreting this excess uric acid is obviated. Excellent illustrations of this phenomenon are presented by Gutman[7] These changes are even more striking than the restorative processes noted in the bones.

The most impressive subjective evidence in support of the value of the combination of colchicine and Benemid is the diminution or elimination of acute articular bouts.[15] Acute attacks have appeared at times in some of the patients, irrespective of the length of time that they have adhered to the colchicine-Benemid regimen. It is somewhat discouraging to the patient to have acute arthritis appear within a few weeks after beginning the daily ingestion of colchicine and Benemid. Once the patient is well established on the regimen, the incidence of acute episodes decreases almost to the vanishing point Patient P.M. is an example. In the summer of 1949, this patient, a member of a gouty family, was confined to bed for almost three months because of migratory gouty arthritis. He was placed on colchicine daily and had one moderate attack of acute gout in 1951. Since Benemid was added to the prophylactic regimen, six years ago, he has lost no time from work. Most patients, irrespective of the severity of the disease, average less than one day per year of incapacity because of acute arthritis if adherence to the prophylactic regimen is consistent This experience represents a striking change from the incidence of attacks in the pre-Benemid period.

Another effect of the combined medication is an improved feeling of well-being, not noted while colchicine was the only drug administered regularly Undoubtedly this euphoria is associated with a reversal of the migration of urates from body fluid to bone and soft tissue. Because of the beneficial features of an abundant fluid intake for most patients with gout, under Benemid maintenance, this aspect of treatment is vital Since the concentration of uric acid in glomerular filtrate is near the saturation level, every effort should be made to provide an abundance of fluid for the kidneys in order to inhibit precipitation of urates in the renal parenchyma

Only three patients have discontinued Benemid during our experience, which has extended over a period of more than seven years. The first patient was 75 years of age and mildly afflicted with gout. He had taken colchicine daily for a number of years and had not experienced any acute attacks and presumably saw no reason for adding another drug at his age Interestingly enough he has had no acute attacks for almost a decade, but he has shown evidence of unmistakable progression of osseous tophi, a progression which, I am confident, would not have occurred had Benemid been accepted. He is now 84 years of age, going strong, and I assume no serious deficiency

11. Reynolds, E. S., Schlant, R. C., Gonick, H. C. and Dammin, G. J. Fatal massive necrosis of the liver as a manifestation of hypersensitivity to probenecid. New England J. Med. *256*: 592, 1957.
12. Schacter, D. and Taggert, J. V. Glycine N-acylase: purification and properties. J. Biol. Chem. *208*: 263, 1954.
13. Sirota, J. H., Yu, T. F. and Gutman, A. B. Effect of benemid (p-(di-n-propylsulfamyl) benzoic acid) on urate clearance and other discrete renal functions in gouty subjects. J. Clin. Invest. *31*: 692, 1952.
14. Talbott, J. H., Gout. New York, Oxford University Press, 1943.
15. Talbott, J. H. Gout. New York, Grune & Stratton. 1957.
16. Wolfson, W. Q., Cohn, C., Levine, R. and Huddlestein, B. Transport and excretion of uric acid in man, physiologic significance of the uricosuric effect of caronamide (Abs.). Am. J. Med. *4*: 774, 1948.

been taken off Benemid for varying periods of time *after adherence to the* regimen for two or more years. These patients have *continued small doses of colchicine from time to time*. Persons mildly afflicted may or may not be placed upon Benemid initially. The tendency at the present time is not to recommend Benemid daily if not more than two or three attacks of gouty arthritis have occurred over a period of several years. If the incidence of acute articular gout is greater than one per year, institution of daily Benemid is recommended. Admittedly, these suggestions for therapy are not particularly precise, but clinical experience has born out the value of these empiric suggestions.

Obviously we are firmly convinced of the prophylactic value of the combination of colchicine and Benemid. More than 100 patients with gout are followed at regular intervals. The majority are on Benemid; those not taking the drug are afflicted with a mild form of the malady. The clinical *results on the regimen during the seven year period are gratifying and represent* the most satisfactory treatment of any type of joint disease. Not only is treatment satisfactory, but the prevention of incapacity and the provision for normal living makes the disease a minor rather than a major problem for the afflicted.

References

1 Austrian, C R and Boger, W P Sensitization and subsequent desensitization to probenecid (benemid). Arch. Int Med *98*: 505, 1956

2 Beyer, K H, Wiebelhaus, V D, Tilson E K, Russo, H F and Wilhoyte, K M · "Benemid," p-(di-n-propylsulfamyl) benzoic acid, inhibition of glycine conjugative reactions Proc Soc. Exper Biol & Med *74*: 772, 1950

3. Boger, W P and Smith, R T · The role of probenecid in the therapy of gout *Translation of an article from Svenska Lakartidningen 51*· 2021, 1954.

4 Boger, W P and Strickland, S. C Probenecid (benemid), its uses and side effects in 2502 patients Arch Int Med *95* 83, 1955

5 Bronsky, D, Dubin, A. and Kushner, D S · Diuretic action of benemid Its effect upon urinary excretion of sodium, chloride, potassium and water in edematous subjects Am J Med *18* 259, 1955

6 Goodman, L S and Gilman, A The Pharmacological Basis of Therapeutics New York, MacMillan, 1955

7 Gutman, A B and Yu, T F. Prevention and treatment of chronic gouty arthritis. J A M A *157* 1096, 1955

8 Kittredge, W. E and Downs, R. The role of gout in the formation of urinary calculi J Urol *67* 841, 1952

9 Pascale, L R, Dubin, A. and Hoffman, W. S: Therapeutic value of probenecid (benemid) in gout J A M A *149*. 1188, 1952

10. Phillips, R W Reversal of renal insufficiency in gout; report of a case treated with probenecid (benemid) Arch Int *Med 96* 823, 1955

ploying heparinized, oxalated or defibrinated blood[1, 14, 16, 46, 50] or blood collected in silicone-coated tubes[16, 47] have also been described and are usually satisfactory. However, the mechanisms involved in the formation of L.E. cells appear to be activated or accelerated by blood coagulation[47, 73] or some related phenomenon, such as the breakdown of platelets[21, 47] or release of a co-factor.[8, 41, 47] The addition of anticoagulants tends to reduce the intensity of the reaction.[46, 47] In lieu of using bone marrow or whole blood from the affected patient, the test may be performed by adding the plasma, serum or serous effusions of the patient to donor cells obtained from bone marrow or peripheral blood of normal subjects,[20, 25] or various laboratory animals such as the dog or guinea pig.[3, 25] This method has some advantage when the patient has a severe neutropenia, or when plasma must be shipped or stored for future study. It also provides a convenient method of studying the phenomena with living cells in wet film preparations.[54, 56, 61] There is no inherent abnormality of the leukocytes which are added to the test serum and their source is not important, although differences in the susceptibility of leukocytes from varying human and animal sources have been observed.[9, 56] In an attempt to enhance the formation of L.E. cells some investigators have advocated the addition of dead cells or nucleoprotein material from other sources, either to the patient's blood in a test tube[46, 54] or on glass slides.[65] Micro-methods have also been described, requiring only a few drops of blood on a glass slide.[62, 64] The breakdown of leukocytes may be augmented by a method which involves rotation of heparinized blood containing glass beads.[77]

Whatever method is employed, it is desirable to obtain an adequate concentration of leukocytes in order to facilitate examination of the stained smear. The optimum period that the specimen should stand before preparing the smears varies from one half to two hours, depending on the intensity of the reaction. Incubation of the specimen at 37°C. will hasten the reaction, but room temperature (22°C.) is usually satisfactory.

THE L.E. FACTOR

The factor responsible for the phenomenon resides within the tissue fluids of the patient and has been shown to be intimately associated with the gamma globulin fraction of the plasma proteins.[3, 50] The exact nature and source of the factor is not known, nor is it certain that it represents a single substance. It can be demonstrated in the plasma, serum, or serous effusions[3, 20, 23, 25, 41, 61] of most patients with systemic lupus erythematosus, and has occasionally been reported in cerebrospinal fluid,[33] urine[27, 44] and in artificially produced blisters.[19] It appears to be stable in sterile solution and can be preserved indefinitely in the frozen state,[3, 23, 44] but is inactivated by bacterial contamination or heating to 65°C.[23] Complement is not neces-

The L. E. Cell Phenomenon

by M. A. Ogryzlo

INITIALLY REPORTED IN 1948 BY HARGRAVES, Richmond and Morton,[23] the recognition of the L.E. cell phenomenon represents a major advance in the evolution of our knowledge of systemic lupus erythematosus. It has served to separate this complex syndrome more clearly from other members of the collagen group of diseases, and may eventually play an important role in the elucidation of mechanisms involved in its pathogenesis. At the same time it has brought to light a number of additional syndromes whose relationship to lupus erythematosus have not yet been clarified

The phenomenon was first observed in bone marrow preparations from patients with systemic lupus erythematosus, but only when the aspirated material had been permitted to stand for a time before smears were prepared It was not found in direct smears of bone marrow. Subsequent studies not only confirmed these observations[31] but showed that identical changes could be induced in samples of whole venous blood[68] The demonstration of the phenomenon is an empirical procedure that depends upon morphologic alterations affecting leukocytic elements after removal from the body and requires a certain time interval to develop. It has been attributed to a component present in the plasma of the patient, called the L.E. factor. Under appropriate circumstances, this factor is capable of inducing degenerative changes in the leukocytes of the blood or bone marrow, resulting in the formation of structures which are distinctive of the phenomenon As commonly performed it represents an in-vitro phenomenon, although it may sometimes be induced in vivo.[11, 58]

METHODS

Many different methods have been described for performing the test. Heparinized bone marrow[23, 31] yields excellent results but has been replaced by procedures which are less distressing to the patient A simple and effective method is to use whole venous blood that has been allowed to clot and stand for a period of time.[44, 49, 75] The serum is removed, and a mixture of cells obtained by compressing or macerating the clot with applicator sticks, or by forcing it through a wire-mesh screen The cells thus expressed are centrifuged in a Wintrobe hematocrit tube at high speed for 5 minutes, after which the buffy coat is removed with a fine glass pipette and smeared on glass slides. Any of the routine blood stains may be used Methods em-

cell membranes rupture and the altered nuclear masses are released. In stained smears these masses can be found singly or in small clusters, sometimes connected by thin filaments indicating their origin from polymorphonuclear leukocytes. They vary in size, shape and staining properties, and while they are usually homogeneous they may occasionally appear somewhat granular. These initial changes which are induced in living cells by the L.E. factor, are undoubtedly the most significant feature of the reaction. They may represent the action of an autoantibody to leukocytes or their nuclei, or an enzymatic effect which alters the permeability of the cell membrane with eventual lysis and depolymerization of the nuclear material.

The second phase of the reaction which is represented by the phagocytosis of the nuclear masses by other viable cells, may be compared to the phagocytosis of any foreign material. When such a nuclear mass is fully enclosed within the cytoplasm of the parent cell, it represents a true L.E. cell. In some preparations fully developed L.E. cells may be scarce or even absent, possibly due to a lack of the normal phagocytic stimulus, although there may be abundant extracellular nuclear material and many viable cells. At the present time the interpretation of such smears is problematical and open to doubt. L.E. cells may contain more than one inclusion body, varying from two to five. In the formation of the rosettes, phagocytosis of larger nuclear masses may be attempted by two or more leukocytes. When surrounded by a collar of cells they present the appearance of a rosette. The parent cell which ingests the nuclear material (to form an L.E. cell) is nearly always a neutrophil, but under appropriate circumstances other cell types may also be phagocytic. Thus, the addition of donor cells from patients containing a high proportion of eosinophils, lymphocytes, monocytes, plasma cells or myelocytes, may result in these cells engulfing nuclear material to form parent L.E. cells.[3, 34]

INTERPRETATION OF THE TEST

As it is now performed, there is no satisfactory method of quantitating the test other than to state that L.E. cells are present in large or small numbers. Actual counts of L.E. cells cannot be regarded as accurate. Smears which do not permit a clear cut interpretation should be reported as doubtful and the test repeated. The recognition of a positive test is not difficult when many L.E. cells are present (more than 2 per cent of the neutrophil count). A positive report may also be based on the finding of L.E. cells in small numbers (less than 1 percent), providing they are morphologically characteristic, and particularly if rosettes or extracellular amorphous masses are present. It should never be based on the finding of a single L.E. cell. Neither can it be made on the finding of extracellular masses and rosettes alone, in the absence of fully formed L.E. cells, although these may be very significant. L.E. cells must be differentiated from phagocytosis of lymphocytic or other

sary for its action. It has also been reported to be inhibited in vitro by manganous ions,[12] paraaminobenzoic acid, and by L E. antibodies developed in rabbits against the specific gamma globulin,[25, 29] but not by cortisone, testosterone, estradiol, progesterone or control antibodies developed in rabbits against normal human plasma.[25] It may be transferred passively to laboratory *animals*[10] *and has been shown to cross the placental barrier in* the human.[5] In one instance the L E test remained positive for a period of seven weeks after delivery, although it was not associated with symptoms of the disease in the infant.

MORPHOLOGY OF THE L.E. PHENOMENON

Three structures are recognized as being characteristic of this phenomenon. (1) the L E cell, (2) the rosette and (3) amorphous, extracellular nuclear material. Typically the L.E. cell is a mature, polymorphonuclear neutrophil containing within its cytoplasm a large, amorphous or homogeneous inclusion body derived from the phagocytosis of altered nuclear material of other cells. The inclusion body, of which there may be more than one, usually displaces the segmented nucleus of the parent cell to the periphery It takes on a homogeneous, reddish-purple color with Wright's stain, is less dense than normal nuclear material and lacks any chromatin detail. In positive smears, nuclear masses identical to the intracellular inclusion bodies are also found extracellularly in varying numbers The rosette consists of a collar of neutrophils surrounding a larger mass of the altered nuclear material While all three structures are usually present in positive smears and may be of equal significance, by *definition a smear may be* called positive only if typical L E. cells are present. The intensity of the reaction will vary from patient to patient and even in different tests performed on the same patient

The source of the inclusion bodies and the extracellular masses has been abundantly confirmed (plates I and II). Differential staining techniques with Feulgen and methyl green indicate a nuclear origin[19, 46] and have shown the desoxyribosenucleic acid to be largely in the depolymerized state. The formation of L E. cells has actually been observed in living, wet-film preparations[54 56, 61] and has been recorded with micro-cinematography[56] Fixed, stained smears, prepared serially at short time intervals, also provide evidence which corroborates the sequence of events.[3 46, 56, 67] The initial changes may be observed within a few minutes of drawing the blood. Some of the neutrophils, lymphocytes and possibly other cells, undergo a form of degeneration, with an alteration in their staining characteristics. The nuclei appear *swollen, stain less intensely and the chromatin* structure becomes less distinct Eventually the nuclei of the affected cells assume a smoky or homogeneous appearance with complete loss of all chromatin detail. Finally the



(a)

(b)

nuclei, in which the chromatin material remains unaltered or is not completely amorphous. These forms are of no significance. Difficulty may also be experienced in recognizing ingested fungus or yeast forms, red cells or precipitated cryoglobulin.[26, 71]

SIGNIFICANCE OF THE L.E. PHENOMENON

The L.E. phenomenon has provided a tremendous stimulus to the study of systemic lupus erythematosus and will undoubtedly influence existing views concerning the incidence, natural history and variable course of this malady. Meanwhile, it has made the diagnosis more decisive in many cases, where formerly it may have been in doubt. The phenomenon can readily be demonstrated in the majority of patients with the acute systemic form of the disease, varying from 60 to 95 percent of cases.[6, 14, 21, 45, 66] Moreover, the incidence of positive tests rises with the number of times that the procedure is repeated, since patients in whom it is negative at one specific period of time, may be strongly positive weeks or months later. Once it has become positive it tends to persist for indefinite periods. However, since the phenomenon cannot be demonstrated in all cases, a negative test does not exclude the diagnosis. In some patients the test has remained consistently negative in spite of classical or even fulminating symptoms, and in whom autopsy examination has provided confirmatory evidence for the diagnosis.[56, 67] It may occasionally be positive in patients with the subacute form of the disease but rarely if at all, in chronic discoid lupus erythematosus.

The intensity of the reaction cannot always be correlated with the severity of the illness or with the level of the white cell count. Greater difficulty may be experienced in obtaining a good concentration of cells in patients with a severe leucopenia, but this can usually be overcome by the addition of donor cells. Neither does it correlate with any particular organ or system involvement, nor with changes in the electrophoretic pattern of the serum proteins. In general, a positive test does not revert to negative, coincident with the clinical improvement that accompanies the institution of therapy with cortisone or related steroid hormones, although transient reversals may occasionally be seen with the use of large doses. It may however revert to negative or become more difficult to demonstrate in a proportion of patients after they have been maintained in a state of partial or complete remission with prolonged steroid therapy, for periods of two to five years.[25, 56] More often the test continues to remain positive regardless of the degree of clinical improvement achieved with this form of treatment. The occurrence of prolonged spontaneous remissions on the other hand are not infrequently accompanied by a reversal of the test to negative. There is no convincing evidence to show that L.E. factor is responsible for the tissue changes occurring in systemic lupus erythematosus, although the so-called "hematoxylin-


(a)


(b)


(c)


(d)


(e)


(f)


(g)


(h)

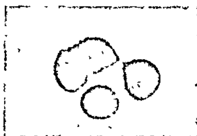
L.E. cells containing multiple inclusion bodies. Successive stages illustrating formation of characteristic rosette.


(a)

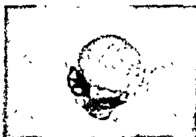

(b)


(c)


(d)


(e)


(f)


(g)


(h)

Successive stages illustrating formation of L.E. cells from neutrophils. L.E. cells tend to clump together

only the characteristic joint deformities and nodules without evidence of visceral disease.[38, 56, 74] A few have been subjected to orthopedic surgical procedures for the correction of severe deformities. Rarely, in patients with rheumatoid arthritis and leucopenia, the test has become positive after the initiation of steroid therapy and at a time when the patients have been greatly improved symptomatically.[58] In others it has become positive during the severe relapse that has followed the withdrawal of steroid therapy.[57] The L.E. phenomenon has occasionally been associated with reactions to various therapeutic agents, including penicillin,[72] phenylbutazone[56] and hydralazine.[15, 56, 58, 60, 64] It is of interest that it has not been observed during reactions to gold in the treatment of rheumatoid arthritis. The reactions to penicillin and phenylbutazone would fulfill the criteria of hypersensitivity phenomena, in that symptoms have come on rather acutely, usually within 10 to 14 days of the institution of therapy. The reactions to hydralazine on the other hand have not appeared early and may represent a manifestation of toxicity or competitive inhibition of a vital enzyme system. They have been encountered in 5 to 8 per cent of patients treated with large doses of hydralazine over prolonged periods for essential hypertension, usually a year or longer. Affected patients have developed either the manifestations of rheumatoid arthritis, or a clinical syndrome resembling systemic lupus erythematosus with demonstrable L.E. cells. Autopsy examination in one such patient failed to disclose tissue changes characteristic of systemic lupus erythematosus.[58] From a pathogenic point of view, it is significant that such instances of iatrogenic disease have been reversible after the withdrawal of the offending agent. The demonstration of the phenomenon in these different diseases does not imply that identically the same factor is responsible in all cases, although the mechanism of production of the characteristic cells may be the same. Not infrequently the intensity of the reaction is less pronounced than is commonly seen in systemic lupus erythematosus, but this does not always hold true.

On the experimental side, structures resembling but not necessarily identical with L.E. cells have been produced with leukocytic antiserum,[17, 6] desoxyribonuclease,[7] polyvinyl alcohol polysulfonic acid ester,[35] and with virus cultures recovered from patients with lupus erythematosus.[34] Attempts to demonstrate the participation of serum desoxyribonuclease in the L.E. phenomenon in patients with lupus erythematosus have not been successful,[42] although a nuclease inhibitor derived from normal human leukocytes has been shown to inhibit the phenomenon.[41] Based on the latter observation, treatment with fresh, compatible blood or leukocyte fractions, administered intramuscularly, has been attempted with some success.[41]

The weight of existing evidence does not permit the assignment of absolute specificity to the demonstration of the L.E. phenomenon although

bodies"[39] appear to represent degenerative changes in mesenchymal cells, comparable to those which occur in-vitro in the L.E. phenomenon.

The specificity of the reaction has been questioned by some observers[6, 38, 43, 56] who have demonstrated the phenomenon in a smaller proportion of other diseases. Nevertheless, many investigators with wide experience continue to regard the test as pathognomonic of systemic lupus erythematosus,[13, 14, 24, 27, 73] with the inference that the initial diagnosis may have been incorrect or that systemic lupus erythematosus may have been coexistent in such cases. This difference of opinion is not in the interpretation of the test itself, but rather in the classification of the cases encountered with a positive L.E. test. In his original report, Hargraves[23] acknowledged that the diagnosis of lupus erythematosus might be questioned clinically in some of the twenty-five patients observed with positive tests. Different authors have reported positive tests in a variety of unrelated diseases, suggesting that the phenomenon may represent an abnormal enzyme reaction[44] or that it may be present in circumstances where there is active destruction of body tissues,[23] disturbances of the antibody-producing mechanism[17, 37, 76] or related to hypersensitivity without exhibiting manifestations of systemic lupus erythematosus.[54, 72] L.E. cells have been reported, though sometimes in small numbers, in isolated instances of leukemia,[45] Hodgkin's disease,[56] multiple myeloma,[52] pernicious anemia in relapse,[3] acquired hemolytic anemia,[44, 56] dermatitis herpetiformis,[3] moniliasis,[15] miliary tuberculosis,[36] periarteritis nodosa,[48, 56] dermatomyositis[50] and scleroderma.[38, 70]

More significantly however, L.E. cells have been reported in a number of disease syndromes, whose relationship to one another and to lupus erythematosus still remains to be determined.[57] Included among these have been a group of patients with a variety of chronic hepatitis[2, 4 34, 37, 58] characterized by prolonged or recurring jaundice and with evidence of severe liver damage. The liver and spleen are usually enlarged and may be associated with oesophageal varices, spider telangiectases, ascites, edema and sometimes joint effusions, hirsutism and amenorrhoea. The gamma globulin fraction of the serum proteins may be considerably elevated. Autopsy examination in such cases has revealed an advanced cirrhosis as the principal change with none of the lesions distinctive of systemic lupus erythematosus.[2, 84] Apart from lupus erythematosus however, the highest incidence of positive tests has been reported in chronic rheumatoid disease,[6, 39, 51, 56, 74] *varying from 9 to 17 per cent of cases.* The patients have exhibited the classical picture of chronic rheumatoid arthritis, present for periods up to 31 years, with gross joint deformities and frequently associated with juxta-articular, rheumatoid nodules. Some of the recorded cases have shown evidence of systemic visceral involvement similar to that which may be seen in other members of the collagen group of diseases,[65] but many have had

17 Finch, S C., Ross, J F. and Ebaugh, F G Immunologic mechanisms of leukocyte abnormalities J Lab. & Clin Med. 42 555, 1953
18. Gausewitz, P L., Jones, F S and Worley, G Fatal generalized moniliasis report of a case Am J Clin Path 21 41, 1951
19 Goeft, B · Depolymerization of nucleic acid in acute disseminated lupus erythematosus Arch Dermat. & Syph 61 892, 1950
20 Hargraves, M M · Production in vitro of L.E. cell phenomenon use of normal bone marrow elements and blood plasma from patients with acute disseminated lupus erythematosus. Proc Staff Meet, Mayo Clin 24 234 1949
21 Hargraves, M. M The L.E cell phenomenon Proc Staff Meet, Mayo Clin 27 419, 1952.
22. Hargraves, M M The L E cell phenomenon In Advances in Internal Medicine, Vol 6, edited by I Snapper and W Dock Chicago, Year Book Publishers 1954
23 Hargraves, M M., Richmond, H and Morton, R Presentation of two bone marrow elements the "tart" cell and the "L.E." cell Proc Staff Meet, Mayo Clin 23 25, 1948
24 Harvey, A McG, Shulman, L E., Tumulty, P A., Conley, C. L. and Schoenrich, E. H. Systemic lupus erythematosus review of the literature and clinical analysis of 138 cases Medicine 33 291, 1954
25 Haserick, J R Blood factor in acute disseminated lupus erythematosus. Arch Dermat & Syph 61: 889, 1950
26 Haserick, J R · Simulation of the lupus erythematosus phenomenon by materials of fungal origin J Invest Dermat 16 211, 1951
27. Haserick, J R Evalution of three diagnostic procedures for systemic lupus erythematosus, Ann Int Med 44 497 1956
28 Haserick, J R and Bortz, D W Normal bone marrow inclusion phenomena induced by lupus erythematosus plasma J Invest Dermat 13 47 1949
29 Haserick J R and Lewis, L. A Blood factor in acute disseminated lupus erythematosus II Induction of specific antibodies against L E. factor Blood 5 718, 1950
30 Haserick, J R., Lewis, L. A and Bortz D W Blood factor in acute disseminated lupus erythematosus I Determination of gamma globulin as specific plasma fraction Am J Med Sc 219 660 1950
31 Haserick, J R and Sundberg R D The bone marrow as a diagnostic aid in acute disseminated lupus erythematosus report on the Hargraves "L E" cell J Invest Dermat 11 209, 1948
32. Hauser, W Nachweiss des L.E. Faktors im Urin bei einer Kranken mit Lupus Erythematodes acutus. Klin Wchnschr 30 39 1952
33 Hauser, W., Uber den nachweis des L.E. Faktors im Liquor Cerebrospinalis bei Lupus Erythematodes cum Exacerbatione acuta des Zentralnervensystems. Med Klin 46 412, 1951
34 Heller, P., Zimmerman H J Rozengvaig S and Singer K The L.E. cell phenomenon in chronic hepatic disease New England J Med 254 1160 1956.
35 Inderbitzin, T The experimental production of leukocytic changes in normal blood similar to L.E.-cells and morphologically identical with L.E. cells. J Invest Dermat 20 67, 1953.
36 Jacobs, A. G. A false-positive lupus erythematosus test. Ann Int Med 42 1037 1955.
37. Joske, R A and King W E. The "L.E cell" phenomenon in active chronic viral hepatitis. Lancet 2 477, 1955

it is most characteristic of systemic lupus erythematosus. For this reason, a strong suspicion should be entertained in favour of the diagnosis of systemic lupus erythematosus whenever a positive test is observed in a patient, particularly if the clinical symptomatology is compatible with this disease. Meanwhile, the fundamental nature of the phenomenon and the factor responsible for its occurrence must await further clarification.

References

1. Barnes, S S, Moffatt, T. W and Weiss, R. S Demonstration of the L. E. cell in the absence of anticoagulant J Invest. Dermat. 14 397, 1950
2 Bearn, A. G, Kunkel, H G and Slater, R J.: The problem of chronic liver disease in young women Am J. Med 21: 3, 1956
3 Berman, L., Axelrod, A R, Goodman, H. L and McClaughry, R. I. So-called "lupus erythematosus inclusion phenomenon" of bone marrow and blood Am J. Clin Path 20· 403, 1950.
4 Bettley, F R "L. E cell" phenomenon in active chronic viral hepatitis Lancet 2· 724, 1955
5 Bridge, R G. and Foley, F E Placental transmission of the lupus erythematosus factor. Am J. Med Sc. 227 1, 1954
6. Brunsting, L A, Stickney, J M, Pease, G. L and Reed, W B: The Clinical significance of the L. E clot test. Arch Dermat. 73: 307, 1956
7. Butterworth, C E, Jr· The production of L. E cells in normal individuals J Clin Invest 32 558, 1953
8 Campbell, E W. and Stefanini, M Isolation and purification of the plasma thromoplastin· its physicochemical and biological properties. Proc. Soc. Exper. Biol. & Med 83 105, 1953
9 Carrerea, A E., Reid, M V. and Kurnick, N B: Differences in susceptibility of polymorphonuclear leucocytes from several species to alteration by systemic lupus erythematosus serum Blood 9. 1165, 1954
10 Castillo, P, Fernandes, L and Remedios, V G: Celulas "L.E" en el curiel· Notra preliminar (the production of L.E cells in guinea pigs) Arch. med int 12. 173, 1952
11. Chomet, B., Kirshen, M M, Schaeffer, G and Mudrik, P· The finding of the L.E. (lupus erythematosus) cells in smears of untreated, freshly drawn peripheral blood Blood 8 1107, 1953
12 Comens, P Manganese depletion as an etiological factor in hydralazine disease Proc. 10th Ann. Meet South Soc Clin. Res Jan 21, 1956, p. 9
13 Conley, C L: The L.E cell test. Bull Rheum Dis 2, (supplement) No 1, 1956
14 Dubois, E. L. Simplified method for the L.E cell test· Results of a three year study of seven hundred tests in many disease states Arch Int Med 92 168, 1953
15 Dustan, H P, Taylor, R D., Corcoran, A C and Page, I H: Rheumatic and febrile syndrome during prolonged hydralazine treatment. J.A.M.A 154· 23, 1954
16 Eppes, W and Ludovic, E· Demonstration of the "L.E" cell without use of anti coagulants Blood 6: 466, 1951

63 Seaman, A J and Christerson, J W.: Demonstration of L.E. cells in pericardial fluid: report of a case J A M A 119 145, 1952
64 Shackman, N H., Swiller, A I and Morrison, M Syndrome simulating acute disseminated lupus erythematosus appearance after hydralazine (Apresoline) therapy J A M A 155 1492, 1954
65 Slocumb, C. H: Rheumatic complaints during chronic hypercortisonism and syndromes during withdrawal of cortisone preliminary impressions Proc Staff Meet., Mayo Clin 28 655, 1953
66 Snapper, I and Nathan, D J The mechanics of the "L.E." cell phenomenon, studied with a simplified test Blood 10: 718, 1955
67 Suksta, A and Conley, C L Some observations on the L.E. cell J Lab & Clin Med 37: 597, 1951
68 Sundberg, R D and Lick, N B "L.E" cells in the blood in acute disseminated lupus erythematosus J Invest Dermat 12 83 1949
69 VanDoormal, T A J. and Schreuder, J T R Über die sogenannte erythematodeszelle und deren vorkommen in der pleuraflussigkeit bei einer an "lupus erythematodes disseminatus acutus (subacutus)" leidenden patientin Dermatologica 101: 167, 1950
70 Volpe, R and Hauch, J T A case of scleroderma with L.E. cells and prolonged remission on cortisone therapy Canad M A J 72 597 1955
71. Volpe, R and Ogryzlo, M A The cryoglobulin inclusion cell Blood 10 493 1955
72 Walsh, J R and Zimmerman, H J The demonstration of the "L.E." phenomenon in patients with penicillin hypersensitivity Blood 8 65, 1953.
73 Weiss, R S and Swift, S The significance of a positive L.E. phenomenon Arch. Dermat 72. 103, 1955
74 Ziff, M: The agglutination reaction as a diagnostic aid in rheumatoid arthritis Bull Rheum Dis. 7 (supplement) No 4 1956
75 Zimmer, F. E and Hargraves, M M The effect of blood coagulation on L.E cell formation Proc. Staff Meet., Mayo Clinic 27 424, 1952
76 Zimmerman H J., Walsh, J R and Heller, P Production of nucleophagocytosis by rabbit antileukocytic serum Blood 8 651, 1953
77 Zinkham, W H and Conley C. L Some factors influencing the formation of L.E. cells a method for enhancing L.E cell production. Bull Johns Hopkins Hosp 98 102, 1956

38 Kievits, J H, Goslings, J, Schuit, H R E and Hijmans, W.· Rheumatoid arthritis and the positive L.E.-cell phenomenon Ann Rheum Dis *15*. 211, 1956

39 Klemperer, P, Gueft, B, Lee, S. L., Leuchtenberger, C. and Pollister, A. W. Cytochemical changes of acute lupus erythematosus. Arch Path *49*· 503, 1950

40 Korting, G W and Schmitz, R., Induktion des Lupus-Erythematodes zellphanomens mittels Urin Dermat. Wchnschr. *125*· 174, 1952

41 Kurnick, N B · A rational therapy of systemic lupus erythematosus Arch. Int Med 97. 562, 1956

42 Kurnick, N. B., Pariser, S, Schwartz, L. I, Lee, S. L. and Irvine, W.· Studies on desoxyribonuclease in systemic lupus erythematosus, non participation of serum desoxyribonuclease in the "L E phenomenon" J Clin. Invest *31*· 1036, 1952

43 Kurnick, N B, Schwartz, L I, Pariser, S and Lee, S L. A specific inhibitor for human desoxyribonuclease and an inhibitor of the lupus erythematosus cell phenomenon from leucocytes J Clin Invest *32*. 193, 1953.

44 Lee, S L A simple test for L E. cells Am J. Clin Path *21*· 492, 1951

45 Lee, S L Clinical experiences with the L.E. cell test. J. Mt. Sinai Hosp. *22*. 74, 1955

46 Lee, S L, Michael, S R and Vural, I L The L E (lupus erythematosus) cell Clinical and chemical studies. Am J. Med *10*· 446, 1951

47 Lee, S L, Schwartz, L I and Pariser, S · Blood coagulation and the L.E. cell phenomenon Blood *9* 965, 1954

48 Lincoln, M. and Ricker, W. A A case of periarteritis nodosa with L E cells; apparent complete remission with cortisone therapy Ann Int Med *41* 639, 1954

49 Magath, T B and Winkle, V Technic for demonstration of "L E" (lupus erythematosus) cells in blood Am J Clin Path *22*. 586, 1952

50 Mathis, H B A simple office procedure for demonstrating lupus erythematosus cells in peripheral blood Blood *6* 470, 1951

51 McCoy, F W, Patterson, M and Freyberg, R. H: A study of disseminated lupus erythematosus diagnosed in patients formerly considered to have rheumatoid arthritis Ann Rheum Dis *14* 415 1955

52. Montgomery, H and McCreight, W G. Disseminated lupus erythematosus Arch. Dermat. & Syph *60* 356, 1949

53 Moolton, S and Clarke, E quoted by Hargraves, M M (see ref. 22).

54 Moyer, J B and Fisher, G S Experimental production of L.E cells Am J. Clin. Path *20* 1011, 1950

55 Ogryzlo, M A Diffuse systemic rheumatoid disease Ann Rheum Dis *12*· 323, 1953

56 Ogryzlo, M. A. The L.E. (lupus erythematosus) cell reaction Canad M.A J *75* 980, 1956

57 Ogryzlo, M A and Smythe, H A Systemic lupus erythematosus and syndromes possibly related Pediatrics *19* 1109, 1957

58 Perry, H M and Schroeder, H A Syndrome simulating collagen diseases caused by hydralazine (Apresoline) J.A M A *154* 670, 1954

59 Rebuck, J W. and Berman, L Experimental production of the L.E phenomenon in the skin of man Proc. Soc Exper Biol & Med *75* 259, 1950

60 Reinhardt, D J and Waldron, J M Lupus erythematosus like syndrome complicating hydralazine (Apresoline) therapy J.A M.A *155*. 1491, 1954

61 Rohn, R J. and Bond, W H Some supravital observations on the "L.E." phenomenon Am J Med *12* 422, 1952

62 Schultz, I, Baum, J and Ziff, M. A new micro method for the L.E cell phenomenon Proc Soc Exper Biol & Med. 83· 300, 1953

SYSTEMIC LUPUS ERYTHEMATOSUS

The disease has been described for over a century. One of the earliest full descriptions with attention to the nervous and mental symptoms was that of Kaposi in 1872.[30] Osler summarized his experience in 1903.[50] These writers noted the neurologic and psychiatric complications but the basis was not clearly understood. Kaposi discussed the psychiatric manifestations,[30] while two of Osler's cases[51] experienced active delirium or attacks of aphasia and hemiplegia. Osler believed that it was "not improbable that the attacks were due to vascular changes in the brain." From the time of the earlier writers in the last quarter of the last century, a slackening of interest in the disease was apparent until 1924.[35] Most of the early published reports concentrated upon the skin manifestations.

In 1935, systemic lupus was rediscovered by Baehr, Klemperer and Schrifrin.[8] They emphasized the clinical features aside from the nervous system. The discovery of the L.E. cell phenomenon in 1948 by Hargraves[22] and his co-workers was of tremendous importance since it enabled the physician to confirm the diagnosis with a precise laboratory procedure. The greatest incidence of systemic lupus erythematosus is in the second, third and fourth decades of life. In the older age groups, symptoms of rheumatoid arthritis may precede the clinical findings of systemic lupus.[17, 36, 55] Many of the cases of systemic lupus erythematosus show sensitivity reactions to sera, drugs, antibiotics and vaccines. The presence of an anticomplementary serologic test for syphilis and the widespread use of antibiotics and sulfonamides, to which many patients afflicted with lupus have been shown to be sensitive, favors the hypersensitivity theory of causation. The findings of the L.E. cells in sensitivity reactions to penicillin is noteworthy.[53]

In the early stages of systemic lupus erythematosus, the general clinical as well as the neurologic manifestations may be misinterpreted and give rise to an incorrect diagnosis and treatment. Recognition of the varied neurologic and psychiatric manifestations of the disease may be helpful in diagnosis. Systemic lupus erythematosus may simulate several other diseases because of central nervous system seizures and mental symptoms. In some instances, the earliest symptoms are those of nervous system involvement. These may be separated into psychiatric and neurologic manifestations. The commonest symptoms of mental derangement are confusion, restlessness, irritability and apprehension.[10, 13] There may be a delirious reaction with or without hallucinations. Excitement, paranoid states and depressions are also described. Brody,[10] in emphasizing the psychological factors associated with systemic lupus erythematosus, assumed that psychological stress situations have been consistent factors in the pathogenesis or exacerbation of the disease.

The Nervous System in the Less Common Collagen Diseases

by Irving Hyman

INVOLVEMENT OF THE NERVOUS SYSTEM in the less common collagen diseases has been noted with increasing frequency as greater attention is given to these maladies. Although acute rheumatic fever and rheumatoid arthritis rightly belong in the collagen disease syndrome, these dyscrasias have been quite stable in their neurologic interest. The less common disturbances,[66] i.e., systemic lupus erythematosus, polyarteritis, dermatomyositis, systemic scleroderma and thrombosis with thromybocytopenic purpura, present varying nervous system complications, and in many instances the nervous system symptoms and signs point to the correct diagnosis, thereby permitting institution of supportive therapy early in the clinical course. These dysfunctions of connective tissue will be discussed principally in relation to nervous system symptoms and signs and alterations in the electrical activity of the brain In many instances, it is difficult to distinguish the neurologic findings because of the similarity in pathologic disturbance Involvement of the nervous system is usually secondary to degenerative and proliferative changes in the smaller blood vessels. These vessels, when occluded, cause ischemic changes in the central nervous system and peripheral nerves[6]

In systemic lupus erythematosus, the lesion in the central nervous system is most apt to be in the cortex, with seizures[19, 23] apparent clinically. Peripheral neuropathy[7] may develop as a minor complication. In polyarteritis,[52] neuropathy is more common, while in dermatomyositis,[27] the skin, and muscle are involved as well as nerves. In scleroderma,[59] the skin and sympathetic nervous system show alteration. In thrombosis with thrombocytopenic purpura,[1] the lesion is in the smaller vessels in the nervous system and the blood-forming organs. In systemic lupus, scleroderma and thrombotic thrombocytopenic purpura, more females than males are affected; in polyarteritis, the reverse is true. The distribution between sexes is approximately equal in dermatomyositis. The course of the various collagen diseases is extremely variable, although the use of steroids has provided temporary relief for varying periods of time. Arthralgia, fever and skin lesions are less critical than involvement of the nervous system, kidneys and heart.[19]

consciousness, delirium and stupor have been observed.[11, 47] Sedgewick and Von Hagen[62] assumed that many of the nervous system symptoms were due to the terminal azotemia. Hallucinations, delusions, confusion and other psychiatric manifestations were noted by them.

The neurologic manifestations can be segregated into those derived from the peripheral nervous system and those from the central nervous system. In the cases reviewed by Harvey, Schulman and Tumulty,[23] more than one third developed a neurologic abnormality. The central nervous system dysfunction usually begins in the acute phase of disease. Only a small percentage of cases show nervous system lesions in the subacute or chronic phase. The nervous system signs usually are regarded as ominous when they appear.

Seizures are the most common nervous system complaint in lupus. They can be divided in four categories: (1) epilepsy preceding the active phase; (2) epilepsy during the active phase, (3) epilepsy during the terminal phase, and (4) no seizures but electroencephalographic changes with synchronous discharges and neuropathological changes. Haserick[24] considered epilepsy an early finding in some cases of lupus; he contended that any patient with seizures might suffer from systemic lupus erythematosus. Convulsions in the active preterminal phase have been observed in the absence of azotemia. Tumulty and Harvey[67] reported seizures in one case with a dural meningioma and in another with an intracerebral hematoma. Vesey and Nelson[70] studied one patient who suffered terminally from seizures without evidence of infection or infarction. Eighteen per cent of Harvey's cases[23] had seizures, three had hemiplegia and one a motor aphasia. A few patients had seizures for a number of years before lupus was recognized. In two thirds of the patients with seizures, systemic lupus alone was responsible. Other causes were azotemia, a meningioma and septicemia. Seizure occurred frequently as a complication of steroid therapy and was accompanied by psychotic behavior in a few instances. A wide variety of neurologic signs was observed by Clark and Bailey[11] in 24 patients. Only two thirds of the total were receiving ACTH at the time the nervous system findings developed. Complaints developed in three after ACTH was begun. Changes in the fundi were reviewed by Wagener.[71] The fluffy exudates resemble those of healed tuberculosis and histologically represent varicose hypertrophy or ganglioform degeneration of nerve fibers. Perivascular hemorrhages and swelling of the optic disc may be found. The changes in the fundi tend to disappear when the acute phase of the disease subsides. Aiello[1] proved that the yellowish-white to white cotton wool patches in the retina were cytoid bodies in the nerve fiber layer of the retina. The localized thickening contains various cell-like forms of vague outline and possessing poor staining qualities. The cytoid bodies are an important finding but are not pathognomonic of systemic lupus erythematosus.

Favorable psychological influences mitigate the severity of the clinical course. In patients with a psychotic reaction, he postulated that its development appeared to have a positive therapeutic effect and served to prevent a fatal outcome. There were six patients in his series with a protracted psychosis who had survived. Each of the 11 patients who had not been psychotic was dead. The patients described by him were thoroughly investigated by psychoanalytic techniques.

Of 40 cases of systemic lupus summarized by O'Connor,[47] 21 had psychotic episodes, five had a severe neurotic personality and 14 were considered normal. The psychotic group had a more severe form of systemic lupus, manifested by length of stay in the hospital and the need for large doses of cortisone to control symptoms. In this group, the psychosis became evident about 12 days after the onset of cortisone therapy. Of the 21 psychotic patients, 18 received cortisone. Of 11 patients who had a psychosis and were later readmitted, only three had a recurrence of their psychosis. Exacerbations in the medical aspect of the illness increased the possibility of a psychosis, but the reverse was not true. The prognosis for the psychotic episode was good when management consisted of general psychiatric care and gradual withdrawal of the steroid. One patient appeared to suffer from schizophrenia initially and later developed manifestations of sytemic lupus erythematosus. In 10 of 11 patients on whom post mortems were performed, there was pathologic evidence of involvement of the nervous system. Of the 11 cases, each had psychiatric or neurologic signs and symptoms.

In one series of 100 patients reported by Clark and Bailey,[11] 17 displayed some neurologic disturbance worth noting. The order of frequency is as follows: convulsions, hemiplegia, diplopia, choked discs, polyneuritis, subarachnoid hemorrhages, nystagmus, vertigo, choreiform movement, monoplegia, paraplegia, quadraplegia, aphasia, intention tremor, facial palsy, cortical blindness and decerebrate state. Mental disturbance from the use of steroids was noted also. Late in the disease, confusion and delirium may be *secondary to azotemia and kidney failure*. In the group of patients reported by Haserick[24] in whom systemic lupus erythematosus was the only demonstrable cause, 14 suffered psychotic reactions. Restlessness, psychosis, euphoria and depression were frequent findings. In each of five of the cases, seizures with psychotic behavior followed an allergic reaction to ACTH and was associated with an exacerbation of the systemic lupus. In the case reported by Daly,[14] confusion, disorientation and difficulty in expression was noted. Daly assumed that the symptoms were caused by a diffuse non-specific encephalitis. Haserick[24] studied 126 patients, of whom 11 had neuropsychiatric care before the appearance of organic *manifestations*. The personalities noted in the various reports were described as cyclothymic, schizophrenic, epileptic and a variety of neurotic patterns. Manic behavior and confusion appeared later in the disease. In the acute phase, irritability, clouding of

despite the use of anticonvulsants. Slurred speech, confusion, exudates in the retina, diminished deep tendon reflexes with some peripheral muscle weakness and wasting were observed on examination. The spinal fluid revealed no cells, the protein content was 56 mg. per 100 ml. The colloidal gold curve was 2222110000. An electroencephalogram showed a diffuse slow wave dysrhythmia (4-7 per second) with a greater involvement over the left hemisphere.

2. Mental Disturbance During Steroid Therapy

A 27-year-old white female experienced transitory migrating joint pains two months after an operation, five years ago. Cough and bloody sputum appeared later. There was a history of a brief schizophrenic-like illness following a delivery several years earlier. She became fatigued, tense and anxious because of her husband's prolonged illness, but she responded to a short period of hospital rest. An L. E. cell preparation was positive and there was a false positive test for syphilis. Treatment with ACTH was begun. Within 12 days she became increasingly upset and expressed visual, auditory and olfactory hallucinations. It was necessary to transfer her to a closed ward for a few weeks after the steroids were discontinued. No further mental reaction to steroid therapy was noted. Electrolyte studies and an electroencephalogram were normal during this last hospitalization.

3. Peripheral Neuropathy

The diagnosis of systemic lupus was made in a 45-year-old man who suffered pleurisy, loss of hair, a rash on the exposed parts of his body and painful knees. He improved on ACTH and later on cortisone. Weakness appeared first in his upper extremities, but because of progressive weakness, he gradually became unable to walk. Examination revealed that his muscles were weak and atrophic. The tendon reflexes were absent and there was impaired reaction distally in the four extremities. Retinal exudates and papilledema were observed. Terminally he was unable to feed himself or to turn over in bed.

4. Terminal Phase

A 21-year-old white female suffered from systemic lupus for more than 3 years. One week before admission she developed weakness and ankle edema. Examination revealed exudates in the fundi. The liver and spleen were enlarged and there was evidence of congestive heart failure. Pitting edema was noted below the knees. A few days after admission she developed seizures. The calcium was 8.9 mg. per 100 ml. and the blood urea nitrogen ranged from 43 to 167 mg. per 100 ml. The chlorides were 111 mEq. The HCO_3 steadily fell from 16.3 to 11.2 mEq. There was an anemia of 2,300,000 red blood cells per cu. mm. with a hemoglobin of 5.8 Gm. The spinal fluid pressure was 26 mm. of water. No cells were found but the proteins were 108 mg. per 100 ml. The colloidal gold curve was 111221100. Despite all attempts at therapy, she continued to have seizures, complained of severe headaches and became comatose shortly before she died.

5. Seizures as an Early Manifestation

A 26-year-old white female was admitted to the Neurosurgical Service in April 1955 with an eight-day history of nausea, vomiting and uncontrolled generalized seizures. She had also developed headache and oliguria. On examination she was drowsy and displayed periorbital edema. The right pupil was larger than the left. She had difficulty

Transient ptosis was noted by various authors.[20, 23] The hemiplegia usually is a terminal event but many occur during the active phase. Jacksonian epilepsy was noted by Osler.[52] Choreiform movements with a terminal basalar meningitis and a right cerebral abscess was noted in the case in which the earliest treatment was for "nerves." Daly[14] described exudates in the fundi, changing reflexes, facial weakness and deterioration.

Peripheral nerve dysfunction, sensory and motor, have been observed in systemic lupus. Complaints of numbness usually precede the development of gross neurologic findings. Heptinstall[27] has described a symmetrical neuropathy, in other reports mixed neuropathies with weakness, impaired sensation peripherally and impairment in the activity of the deep tendon reflexes have been observed. Mononeuritis and monoradiculitis multiplex have been described. Although peripheral neuropathy has been noted to be a prominent finding, myalgia also has been observed.[14, 55] An unusual complication of the spinal cord secondary to thrombosis of the meningeal vessels which extended to the lumbar cord, was presented by Piper.[55] Other observers have demonstrated ataxia, monoparesis, aphasia, chorea and peripheral neuropathy in patients with lupus.

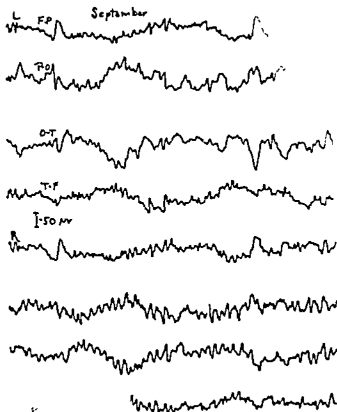
The spinal fluid has not been studied as extensively as other body fluids. The protein content of the spinal fluid in systemic lupus has ranged from normal to a recorded figure greater than 930 mg. per 100 ml. There may be an increase in white cells of the spinal fluid with the increase noted in both polymorphonuclears and lymphocytes. In those patients in whom spinal fluid studies have been done during the active phase, an elevation of protein was usually over 50 mg per 100 ml. Changes in the colloidal gold curve are also observed in some instances.

Electroencephalograms have been performed in relatively small numbers of the reported cases. Three to seven per second moderate high voltage delta waves with asynchrony and six to eight per second medium voltage waves and normal alpha patterns between the slow forms have been described. In one series of 11 cases,[24] there were five patients with seizures without other nervous system findings; two showed abnormal records. More study is indicated in this field. It has been noted that most of the patients had abnormal records in the terminal phase and normal records in a period of remission. A study of the last 24 cases admitted to the Buffalo General Hospital suffering from lupus showed nine in whom there was evidence of a nervous system disturbance. In two of these patients, the nervous system complaints were observed in the terminal phase.

1 Active Phase Without Azotemia

A 47-year-old white female was admitted with the complaints of headache and tender muscles. The red cells and electrolytes in the blood were normal. Seizures persisted

...nstall and Sowry[27] found patchy loss of fibers in the peripheral ... thickening of the endoneurium. The blood vessels in the epi... areas of occlusion with recanalization. There was intim... preservation of the internal elastic membrane. Bailey ... demonstrated degeneration of the posterior root ga... diffuse degeneration of the posterior columns of the sp... cell changes, small to medium sized areas of degen... chronic arteritis were found in the vessels of the ep... Saver[44] demonstrated wedge-shaped military infarcts ... necrosis to gliosis. These changes corresponded to ... which varied from acute fibrinoid degeneration of th... hemorrhagic thrombi to chronic hyalinization of th... thrombi



...ken five months later showing high voltage slow waves and some

in using her right upper extremity purposefully, although strength was good The blood pressure was 190/130 The urine revealed albumin, casts and red blood cells A tentative diagnosis of acute glomerular nephritis was made The patient reported a rash on her right hand for a year and a malar flush was noted An L.E cell preparation was markedly positive. The laboratory studies showed a persistent abuminuria, elevation in the blood urea nitrogen and an anemia The electroencephalogram showed a diffuse slow wave abnormality. (figs 1 and 2)

On anticonvulsants, fluids and steroid therapy, she improved temporarily but was admitted for seizures five times in the following year Blurring of vision and pyelitis were noted, dyspnea became marked A grade IV hypertensive retinopathy with hemorrhages and small atrophic white patches (cytoid bodies) were described During her last admission there was severe congestive failure, a rising blood urea nitrogen and acidosis

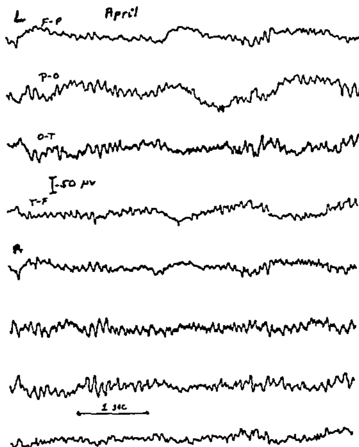


FIG 1 EEG during a remission of a patient with systemic lupus erythematosus.

In recent years there has been general agreement regarding pathologic processes underlying the central and peripheral nervous system changes. Hep-

plicated in human sensitivity reactions. These include the sulfonamides, salicylates and the antibiotics. Some authors have considered the increase in cases of polyarteritis and other collagen diseases to be secondary to the widespread use of antibiotics and sulfonamides.

In a study by Kernohan[72] of the pathology of polyarteritis, the muscles were involved in 30 per cent of the cases, the nerves in 20 per cent and the central nervous system in 8 per cent. From several studies of large groups of cases, a high percentage of nervous system involvement has been demonstrated consistently. From a review of 300 cases, Malamud and Foster[43] tabulated the various nervous system findings as follows:

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The spinal fluid was altered as follows: elevated pressure—11 per cent, elevated protein—9 per cent; increased WBC—6 per cent, and increased lymphocytes—5 per cent.

Liversedge and Leather[39] reported a case of severe generalized polyneuritis with albumino-cytologic dissociation which developed during the course of polyarteritis. Both conditions responded to steroid therapy. Bilateral deafness secondary to polyarteritis has been observed in an adult. Most authors caution against inclusion of the results of the terminal azotemia as a direct central nervous system effect of polyarteritis. There may be a higher percentage of involvement of nerves recorded because these are not examined in many instances. Occlusion of the nutrient arteries on the nerve trunk with infarction in the nerve bundles has been demonstrated as the cause for the neuropathy. The arteritis in the brain may give rise to various findings, depending upon the site of involvement. Multiple arteritis of the cerebral and meningeal vessels may lead to a group of signs and symptoms resembling meningeal encephalitis or syphilis of the nervous system. In a patient with seizures of undetermined etiology, polyarteritis must be considered.[42, 44]

Glaser[20] reported the findings in 18 patients who had died. Lesions of the nervous system were observed in the six in whom autopsies were performed. In three, the lesions were widespread. In one case with a negative neurologic examination, there were multiple areas of focal atrophy of the cortex with some lesions extending into the white matter. In the arterioles, there was intimal proliferation with fibrinoid material extruding from the adventitia through the media to the intima In a second case with a spastic right lower extremity and a flaccid left lower extremity, there were atrophic areas in the frontal gyri with lesions in the blood vessels in these areas There were widespread areas of degeneration and edema in the gyri with ischemic necrosis of the neurons. In the third case with delirium, the lesions were chiefly in the frontal, parietal and temporal areas with a few large hemorrhagic foci which involved chiefly the cortex. There was widespread ischemic degeneration and loss of neurons In the cases without nervous system signs or symptoms, arteritis in the smaller vessels was the most common finding. As in the peripheral nerves, the essential change is vascular, with secondary disturbance of the blood supply to a region. In Piper's case,[55] there was spinal cord swelling and degeneration due to vasculitis with thrombosis of the vessels supplying the meningeal vessels of the spinal cord

There is no specific therapy for the nervous system complications of systemic lupus erythematosus. Supportive therapy is pursued by removal of sources of infection, avoidance of fatigue, physical therapy for the peripheral neuropathy or hemiplegia, adequate dietary intake and clarification of psychological problems whenever possible. Steroid therapy has been shown to produce a temporary remission in systemic symptoms in approximately two thirds of the early cases. When steroid therapy is employed the L. E cell may be found despite clinical improvement; hence, the test cannot be used as the sole guide for treatment.

POLYARTERITIS

This disease was described first by Kussmaul and Maier[34] in 1866 as periarteritis nodosa. Talbott[66] prefers the designation polyarteritis because of involvement of all coats of the vessel walls and the infrequent finding of the nodular lesions There are some objections to the term polyarteritis because the veins may also be involved Perhaps polyangiitis would be a more acceptable term. This disease occurs three times more frequently in males than females and involves both colored and white races Although the onset may be in the extremes of ages, the usual onset is between the ages of 20 and 50. At times polyarteritis may mimic rheumatoid arthritis, acute rheumatic fever, systemic lupus and dermatomyositis.[45] Rich and co-workers[58] produced a syndrome in rabbits similar to polyarteritis in humans by rendering the rabbits hypersensitive to horse serum. Various agents have been im-

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In polyarteritis, Kernohan[32] divided the course into two phases: (1) the fundamental phase in which the small blood vessels are involved in various organs and parts of the body, and (2) the effect of the diseased blood vessels on the tissues they supply. In the blood vessels there is hilar necrosis of a portion of the media and internal elastic lamina and an extensive inflammatory process which extends to the adventitia. Proliferation of the intima produces narrowing of the lumen. Not all vessels are involved and only short segments of a particular blood vessel may show a disturbance. Aneurysms occur with polyarteritis and may rupture The clinical course of a patient with polyarteritis may be extremely slow, with exacerbations and remissions. The progress depends upon the blood vessels involved. Those with cerebral blood vessel involvement may show serious derangement of function, whereas an isolated peripheral nerve lesion is only partially disabling. In elderly patients, polyarteritis may be confused with cerebral arteriosclerosis[9, 60]

POLYARTERITIS WITH PERIPHERAL NEUROPATHY AND TERMINAL BRAIN HEMORRHAGE

A 34 year-old woman was admitted in 1954 with a history of having suffered from bronchial asthma and having been placed on steroids for treatment She had noticed swelling of first one foot, then the other The muscles were sore and stiff. It was difficult for her to go up and down stairs, she complained of numbness of the feet, and the "pins and needles" sensation was disturbing to her. A week before admission she noted numbness of the hands, she lost the use of her fingers, and she was unable to pick up objects Examination at that time revealed impaired sensory perception in the distribution of the left median nerve Later, she complained of headache and experienced difficulty in vision There was slight weakness of the right foot and the left great toe and impaired sensation of the left foot to the ankle. The right hand was improving The blood pressure at that time was 180/110 The right disc was pale and she was placed on steroids and medication to control blood pressure. She died having suffered a left hemiplegia and severe headache before death

The post mortem showed small kidneys. The capsules stripped with difficulty and had scattered areas of hemorrhages over the surface The skin and subcutaneous fat showed lesions typical of polyarteritis with thrombosis of the lumen of the small arteries and fibrinoid degeneration The arterioles of the muscles showed old inflammatory changes. The brain showed the right hemisphere to be larger than the left and the convolutions flattened The small blood vessels were congested In the right basal ganglia there was a massive hemorrhage which measured 7 x 5 5 cm It dissected through the internal capsule into the third ventricle (fig 3) The adjacent brain tissue was soft and scattered with small petechial hemorrhages

DERMATOMYOSITIS AND SYSTEMIC SCLERODERMA

Many authors consider dermatomyositis and systemic scleroderma together. Polymyositis may occur with scleroderma or dermatomyositis and have skin changes resembling those of scleroderma.[4] Scleroderma may reveal Raynaud's phenomenon, a sympathetic nervous system manifestation. In dermatomyositis, there is minimal central nervous system involvement in most instances. Lesions usually are confined to the muscles and skin but oc-

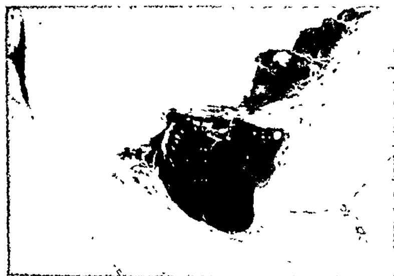


FIG. 3 Terminal ganglionic hemorrhage in a case of polyarteritis

casionally the peripheral nerves are involved.[2] Andrews[5] indicated that the differentiation between dermatomyositis and systemic scleroderma by skin and muscle biopsies continues to offer difficulty.

Dermatomyositis was described by Wagner[74] in 1886 and shortly afterward by Unverricht[69] and Hepp.[20] Adams, Denny-Brown and Pearson[2] believed that the several hundred cases reported prior to 1953 probably represented only a small fraction of the total number affected. Various terms such as neuromyositis, polymyositis, neurodermatomyositis and dermatomyositis have been applied to this disease of unknown etiology, acute, subacute or chronic in nature and characterized usually by an acute or gradual onset with edema, dermatitis and multiple muscle inflammation.[20]

In a review of dermatomyositis in children, Wedgwood, Cook and Cohen[75] observed several sensitivity reactions with skin and muscle changes. Penicillin and sulfonamide derivatives seem to dominate a list of inciting agents, which includes exposure to physical agents, salicylates, bacterial, parasitic and viral agents.[76] No specific factor can be implicated. Any age group can be attacked and the onset may involve the skin, muscles, joints or the nervous system. The muscles are painful and stiff. The proximal muscles are involved early. The process usually is bilaterally symmetrical but it may progress on one side faster than the other. There may be a rash with erythema or it may be papular or macular and involve the face, eyelids, scalp, hands and upper extremities.[44] Hyman, Arlesman and Terplan[23]

have noted a burning painful type of rash. A low-grade fever and photosensitivity may be present. The rash usually appears in the areas exposed to sunlight.[40, 63] In the acute cases, respiratory and bulbar involvement may hasten death. In the subacute variety, the muscles lose volume and become hard and fibrotic, with contractures of the joints and skin In the chronic form, fatigue may be an early symptom, so that myasthenia gravis is suspected No muscles are exempt, including those supported by the cranial motor nerves The heart muscle may be involved. There may be normal skin over diseased muscles and vice versa. A relationship between dermatomyositis and carcinoma has been emphasized in the literature.[15]

Various types of involvement of the nervous system have been observed. In the group of neurodermatomyositis, peripheral neuropathy is prominent. In the case reported by Kinney and Maher,[31] there was a collection of lymphocytes and plasma cells in the perineurium and perivascular connective tissue of the femoral nerve. Other nervous system complaints have included delirium, ocular muscle palsies and optic neuritis. Pleocytosis and increased spinal fluid proteins have been observed as well as a change in the electroencephalogram during the acute phase of the disease. In the cases reported by Wedgewood,[74] the sedimentation rate was elevated in 12 out of 19 patients The spinal fluid studies were normal Only one patient had an abnormal electrocardiogram The most useful laboratory test in confirmation of a clinical diagnosis is a muscle biopsy.

Dermatomyositis with Delirium

A 24 year-old woman was delivered of a baby in September, 1954 Because of an episiotomy she was given penicillin by injection Then ten days later she developed a typical serum sickness like penicillin reaction with generalized hives and swelling She was given ACTH daily for seven days followed by an antihistaminic Gradual improvement in symptoms was experienced On October 20, she complained of headache attributed to a sinus infection A sulfonamide was administered for three days and stopped when there was no evidence of sinusitis She continued to experience frontal headaches and on November 5, had diplopia, on left lateral gaze She became very tremulous and there was a painful burning rash on her forearms and in the axillae.

Neurologic examination revealed a coarse nystagmus in all directions There was a left external rectus weakness She was extremely tremulous and alternations were done poorly Heel-to-shin and finger-to-nose tests were performed with a great deal of hesitation and tremor She walked on a wide base and her Romberg was positive All the deep tendon reflexes were hyperactive but the plantar responses were normal Sensory examination was normal

The rash spread over the entire body shortly after admission She was nauseated and confused but was aware that she was talking to people who were not there She cried aloud and talked almost inaccessently The suggestion of a collagen disease was entertained and steroid therapy instituted A few days later her skin cleared somewhat but she was delusional and hallucinating A few days later she seemed to be clearing mentally and improving neurologically, hence, the steroid dose was reduced. There was a rapid increase in skin symptoms and she said repeatedly that the skin *did not*

itch but felt as though it were burning A skin and muscle biopsy showed the typical lesions of dermatomyositis

The laboratory studies initially showed 92 mg per 100 ml of protein in the spinal fluid with 12 cells, mainly lymphocytes The number of cells in the spinal fluid increased as did the protein content during the acute phase of her illness with a gradual return to normal The electroencephalogram showed a marked slow wave disturbance (fig 4) which gradually returned to normal as her condition improved At the present time she is symptom free and has a normal electroxncephalogram

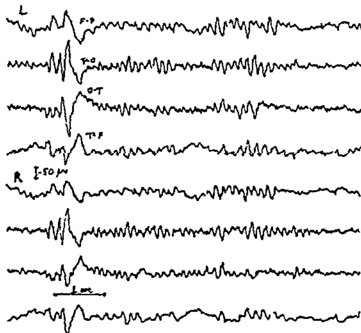


FIG. 4 Slow activity and high voltage paroxysmal bursts in a patient with dermatomyositis during the acute phase

THROMBOSIS WITH THROMBOCYTOPENIC PURPURA

Thrombosis with thrombocytopenic purpura has been included in the collagen diseases by Talbott[96] and others.[1, 23, 45] The cardinal features of this illness are anemia, thrombocytopenia and involvement of the nervous system.[25, 44, 73] The nervous system findings may be extremely severe and overshadow temporarily the other aspects of the disease. The cause is unknown but as in polyarteritis and dermatomyositis, an immuno-allergic basis has been considered. There is a subintimal swelling in the smaller vessels and a smudgy deposit of eosinophilic material Later there is swelling of the endothelium and small areas of rupture of the material where deposits of platelets

and thrombosis occurs. Diffuse involvement of the nervous system, which accounts for the catastrophic type of course, is to be expected.

Single case reports have emphasized seizures or paralysis as an early manifestation. Vertigo, confusion, restlessness and coma have been reported The clinical features include signs of hemorrhagic disease, anemia and neurological symptoms. This disease is more common in adolescence and young adults and affects females more often than males. The neurological symptoms may appear at the beginning of the disease or they may develop later. Death has occurred in from one to four weeks. In the series reviewed by Adams and his co-workers,[1] 12 out of 13 patients revealed neurologic signs. There was an alteration of consciousness in the following range: restlessness, irrational behavior, confusion, delirium, stupor and coma Motor paralysis was present in one-half of the cases and a facial weakness, either peripheral or supranuclear was noted. Status epilepticus was reported and there were other signs of focal lesions with agnosia, apraxia and aphasia. Evidence of peripheral neuropathy was also present. The neuropathologic description included cellular hyperplasia, thrombosis with thrombi of agglutinated platelets and foci of nerve cell damage in the cortex, basal ganglia and brainstem and petechial hemorrhages.

THROMBOSIS WITH THROMBOCYTOPENIC PURPURA IN SIBLINGS

It was our privilege to observe the sister of a patient who had died with this disease She was seen in June, 1955 and complained of double vision intermittently for five years She noted that the periods of double vision were becoming longer and there was some blurring of vision She also complained of increased thirst and nocturia She had poor coordination of her hands with tremors that were embarrassing to her when she tried to pick up objects or drink liquids At times, there was some swelling of the hands and she was unable to bend her fingers to make a fist She had always noted a tendency to bleed easily and told us that her sister died of thrombotic thrombocytopenia with purpura On examination, she had a coarse irregular tremor of the outstretched fingers with loss of check and she performed alternation poorly. She was in the hospital briefly and showed normal skull films, a normal spinal fluid and an electroencephalogram that was within normal limits

Six weeks later she was readmitted with nausea, emesis, purpura and marked anemia She was confused, there were focal and generalized motor seizures and apprehension regarding her fate when she compared herself to her sister There was a gradual decrease in awareness, seizures became more frequent, she went into coma and died At post mortem she showed jaundice and many petechial hemorrhages throughout the body The brain showed focal scattered vascular lesions of the arterioles in the meninges (fig 5) and deeper parts of the brain substance There was a slight subarachnoid hemorrhage The bone marrow showed hyperplasia with the usual number of megakaryocytes being present During her hospital stay she had a blood count of 2,500,000 red blood cells per cu mm with a reduced number of platelets; later her blood count fell to 1,800 000 red blood cells per cu. mm. with 5 Gm of hemoglobin



FIG 5 Thrombosis with thrombocytopenic purpura showing thrombosis with organization in a meningeal vessel

ELECTROENCEPHALOGRAPHY

The involvement of the central nervous system as determined by electroencephalographic changes has been investigated by a number of authors.[77, 83, 85, 87] In a study of rheumatic fever by Lam and Tyler,[85] there were 14 cases with chorea who showed abnormally slow frequencies with improvement during a remission. Of the 14 without chorea 6 had abnormal slowing correlated with hypotonia and decreased tendon reflexes. In 3 cases, serial electroencephalograms correlated well with improvement of the clinical state. It was suggested that the electroencephalograms are evidence of a diffuse cerebral involvement. Lewis, Sinton and Knott[87] studied the electroencephalograms and spinal fluids of patients suffering from a variety of collagen diseases. Fifty-three per cent had abnormal records while 43 per cent showed focal patterns. In 43 per cent, there were changes in the spinal fluid proteins or the colloidal gold reactions. In nine of the eleven patients with systemic lupus, abnormal records were observed. Two of their five patients with dermatomyositis had abnormal records.

In a review of 53 cases with collagen disease, Krump[83] did not consider the bioelectric potentials to be specific. With abatement of symptoms the electroencephalogram improved but under treatment with ACTH, some im-

proved while others worsened. The major finding in the electroencephalogram was slow wave activity with some paroxysmal bursts. It may not parallel the clinical findings If mental changes developed during ACTH therapy, the electroencephalogram revealed delta paroxysmal bursts with beta rhythms in the rolandic areas. During the active phase of the disease, slow waves were present in most instances. Pine and Engel,[54] in a study of electroencephalograms of 32 cortisone and ACTH treated patients, noted that a few became abnormal during treatment but one was considered to be due to the advancing disease process. There was no correlation between the electroencephalogram and electrolyte disturbances. In four patients with alkalosis and hypokalemia, no consistent electroencephalographic findings were noted. They concluded that the electroencephalographic changes could not be specifically related to the effect of adrenal hormone therapy. One group of patients[18] who received cortisone had only a slight increase in the alpha frequency and a tendency toward a normal record. With metrazol activation, it was observed that cortisone did not decrease the cerebral convulsive threshold significantly. Wayne[73] studied the records of 43 patients without obvious metabolic or emotional pattern. He believes that the stability of the pretreatment electroencephalogram is imporant in prognosis. Electrolyte balance, a stable personality structure and absence of stress were other considerations. Most of the patients with a collagen disease had an abnormal record. Russell and his co-workers reported that seizures diminished during steroid therapy while others have not noted any change. In the study by Russell, Haserick and Zucker,[61] abnormal records were found in seven of *eleven patients In the five patients with seizures* the electroencephalograms were abnormal. Of the six patients without nervous system mainifestations, only two records were abnormal. Abnormal records consisted of high voltage asynchronous five to seven per second frequencies or moderate voltage six to eight per second frequencies interspersed with normal alpha patterns The most common electroencephalographic abnormality was a slow delta frequency, diffuse and asynchronous It was noted that all of their patients in remission had a normal record while in the terminal phase all the records were abnormal

References

1 Adams, R P., Cammermeyer, J and Fitzgerald, P. J: Neuropathological aspects of thrombocytic acroangio thrombosis; clinico-anatomical study of generalized platelet thrombosis J Neurol., Neurosurg & Psychiat. *11*, 27, 1948

2 Adams, R P, Denny-Brown, D and Pearson, C. M.: Disease of Muscles New York, Hoeber, 1953

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References

1 Adams, R P, Cammermeyer, J and Fitzgerald, P J. Neuropathological aspects of thrombocytic acroangio thrombosis, clinico anatomical study of generalized platelet thrombosis J Neurol, Neurosurg. & Psychiat. 11: 27, 1948

2 Adams, R P, Denny Brown, D and Pearson, C M. Disease of Muscles New York, Hoeber, 1953.

Aiello, J S. Ocular findings in lupus erythematosus Am J Ophth 35 837, 1951
Allen, W: Dermatomyositis or scleroderma? Arch Dermat & Syph. 19 265, 1929
Andrews, G L. Scleroderma, dermatomyositis Arch Dermat & Syph. 65 210, 1952
Baehr, G, Klemperer, P and Schifrin, A A diffuse disease of the peripheral circulation Tr A Am Physician 50 39, 1935
Bailey, A A, Sayre, G P and Clarke, E. C: Neuritis associated with systemic lupus erythematosus Arch Neurol & Psychiat 75 251, 1956
Bauer, W and Clark, W S Central nervous system in disorders of collagen Arch Int Med 93 315, 1954
Boyd, L. J The cerebral and ocular manifestation of periarteritis nodosa Bull New York M Coll 6 130, 1943
Brody, S Psychological factors associated with disseminated lupus erythematosus Arch. Neurol & Psychiat 70 1912, 1953
Clarke, E C and Bailey, A A Neurological and psychiatric signs associated with systemic lupus erythematosus J A M A 160 455, 1956
2. Clinton H E and Krause, L. A M Acute lupus erythematosus disseminatus Ann Int Med 19 843, 1943
3 Cluxton, H E and Krause, L A M Acute lupus erythematosus disseminatus, Arch Int Med 19 843, 1943
4 Daly, D Central nervous system in acute disseminated lupus erythematosus J Nerv & Ment Dis 102 461 1945
5 Denny Brown, D Primary sensory neuropathy with muscular changes associated with carcinoma J Neurol, Neurosurg & Psychiat 11 73, 1948
6 Dubois, E L The effect of the L. E cell test on the clinical picture of systemic lupus erythematosus Ann Int Med 38 1265, 1953
7 Fox, R A and Rosahan, P D The lymph node in disseminated lupus erythematosus, Am J Path 19 73, 1943
8 Friedlander, W J and Rottger, E. The effect of cortisone on the EEG EEG & Clin Neurophysiol 3 311 1951
9 Glaser G H Lesions of the central nervous system in disseminated lupus erythematosus Arch Neurol & Psychiat 67 545, 952
0 Glaser, G H Neurologic manifestations in collagen diseases Neurology 5 751 1953
1 Glaser, G H and Merritt H H Effect of corticotropin, ACTH and cortisone on disorders of the nervous system J A M A 148 898, 1952
2 Hargraves M M Richmond H and Marton, R Presentation of two bone marrow elements The "Tart" cell and "Lupus Erythematosus" cell Proc Staff Meet Mayo Clin 23 25 1948
3 Harvey A McG Shulman, L. E., Tumulty, P A., Conley C L. and Schoenrich E. H Systemic lupus erythematosus Medicine 33 291 1954
4 Haserick, J R Modern concepts of systemic lupus erythematosus J Chron Dis 1 317, 1955
5 Heffner, Reid R., Kahn, F E and Schraft W C., Jr Thrombotic thrombocytopenic purpura New York J Med 54 111, 1954
6 Hepp, P Ueber Pseudo trichinose, eine besondere form von acuten parenchymatoser polymyositis, Klin Wchnschr 24 297 1887
7 Heptinstall R H and Sowry G S C Peripheral neuritis in systemic lupus erythematosus Brit M J 1 525, 1952
8 Holmes, J M A case of acute dermatomyositis, Brit M J 2 511 1948.

29 Hyman, I, Arbesman, C E and Terplan, K L: Dermatomyositis following penicillin injection Neurology 6. 63, 1956.

30 Kaposi, M H. Neue Beitrage zur Kenntniss des lupus erythematosus Arch f Dermat u. Syph *4* 36, 1872

31 Kinney, T. D and Maher, M M Dermatomyositis. Am J. Path *16* 561, 1940

32 Kernohan, J W and Woltman, H W: Periarteritis nodosa Arch Neurol. & Psychiat *39* 655 1938

33 Krump, J E. Modifications electroencephalographiques des Maladies du collagen. Rev Neurol 92 593 1955

34 Kussmaul, A and Maier, R.· *Ueber eine bisher nicht beschriebene eigenthümliche* Arterienerkrankung (Periarteritis nodosa), die mit Morbus Brightii und rapid fortschreitender allgemeiner Muskellahmung einhergeht Deutsches Arch klin Med *1* 484, 1866

35 Lam, R L and Tyler, H R The EEG in chorea and rheumatic fever FEG & Clin Neurophysiol *3* 374, 1951

36 Leikola, E. and Vartica, K O Lupus erythematosus disseminatus. Acta rhem Scandinav *1* 73, 1951

37 Lewis, B I, Sinton, O W. and Knott, J P.: Central nervous system involvement with disorders of collagen Arch Int Med *93* 315, 1952,

38 Libman, E and Sacks, B A hitherto undescribed form of valvular and mural endocarditis Arch Int Med *33* 701, 1924

39 Liversedge, L A and Leather, H M Corticotrophin treatment in polyneuritis with periarteritis nodosa Lancet *2*, 1241, 1953

40 Logue, R B and Mullin, F Polyarteritis nodosa Ann Int Med *24*. 11, 1946

41 Lovshin, L and Kernohan, J W Peripheral neuritis in periarteritis nodosa Proc. Staff Meet, Mayo Clin *24* 48, 1949

42. Lowman, E W and Slocumb, C H The peripheral vascular lesions of lupus erythematosus Ann Int. Med *36* 1206, 1952

43 Malamud, N and Foster, D B Periarteritis nodosa with special reference to the nervous system Arch Neurol & Psychiat *47* 5, 1942

44 Malamud, N and Saver, G Neuropathologic findings in disseminated lupus erythematosus Arch Neurol & Psychiat *71* 723, 1952

45 Meller, H Polyarteritis nodosa Practitioner *172*· 133, 1954

46 Moschcowitz, E V An acute febrile pleiochromic anemia with hyaline thrombosis of the terminal arterioles and capillaries· an undescribed disease Arch Int. Med *36* 89, 1925

47. O'Connor, J F Psychiatric manifestations in patients with systemic lupus erythematosus Arch Neurol & Psych *77* 166, 1957

48 O'Leary, P A Dermatomyositis M Clin North America *33* 21, 1949

49. O'Leary, P A and Waisman, M · Dermatomyositis Arch Dermat & Syph. *41* 1001, 1940

50. Osler, W On the visceral complications of erythematosa exudativum multiforme Am J M Sc *110* 629, 1895

51. Osler, W On the visceral manifestations of the erythema group of skin diseases Tr A Am Physician *18* 559, 1903

52 Parker, H. L and Kernohan, J W The central nervous system in periarteritis nodosa Proc Staff Meet., Mayo Clin *24*. 43, 1949

53 Paull, A M Occurrence of the L E phenomenon in a patient with a severe penicillin reaction New England J Med *252*. 128, 1955

54 Pine, L, Engel F L and Schwartz, T B The EEG in ACTH and cortisone treated patients EEG & Clin Neurophysiol *3* 701, 1951

55. Piper, P P Disseminated lupus erythematosus with involvement of the spinal cord J A M A *153* 215, 1953

56 Rein, C R and Kostant, G H Lupus erythematosus serologic and chemical aspects. Arch Dermat & Syph *61* 898, 1950

57 Rich, A R The role of hypersensitivity in periarteritis nodosa, Bull Johns Hopkins Hosp *71* 123, 1942

58. Rich, A R and Gregory, J E The experimental demonstration that periarteritis nodosa is a manifestation of hypersensitivity Bull Johns Hopkins Hosp *72* 65, 1943

59 Richter, R B Peripheral neuropathy and connective tissue diseases J Neuropath & Exper Neurol *13* 169 1954

60 Runyan, J W, Jr and Beebe, R T Polyarteritis nodosa Practitioner *12*, 101, 1951

61 Russell, P W, Haserick J R and Zucker E M Epilepsy in systemic lupus erythematosus Arch Int Med *88* 78, 1951

62. Sedgwick, R P and Von Hagen, K P Neurological manifestations of lupus erythematosus and periarteritis nodosa Bull Los Angeles Neurol Soc *13* 129, 1948

63 Sheard, J C Jr Dermatomyositis Arch Int Med *89*: 640, 1951

64 Soffer, L S, Levitt M F and Baehr, G Use of cortisone and adrenocorticotropic hormone in acute disseminated lupus erythematosus Arch Int Med *86* 558, 1950

65 Sommerat, S and MacGillavray W F Thrombotic thrombocytopenic purpura New England J Med 255 585 1956

66 Talbott, J, H and Ferrandis, R M Collagen Disease New York, Grune & Stratton 1956

67 Tumulty, P A. and Harvey A. McG The clinical course of disseminated lupus erythematosus, Bull Johns Hopkins Hosp *85*, 47, 1949

68 Turner, J C, Dermatomyositis New England J Med *216* 156 1937

69 Unverricht, H Polymyositis acuta progressiva Ztschr klin Med *12* 533 1887

70 Vesey, J M and Nelson, H G, Acute disseminated lupus erythematosus. Ann Int Med 32 565 1950

71 Wagener H P Retinal lesions in acute disseminated lupus erythematosus. Am. J M Sc *211* 240, 1946

72 Wagner F Ein fall von acuter Polymyositis Deutsches Arch f Klin Med *11* 211, 1886.

73 Wayne H L Convulsive seizures complicating cortisone and ACTH therapy J Clin Endoc & Metab *14* 1039, 1954

74 Wedgewood, R J P, Cook, C O and Cohen J Dermatomyositis. Pediatrics *12* 447, 1953

75 Wyatt J P and Lee R S Hemorrhagic encephalitis due to disseminated thrombocytic thrombosis Arch Path *49* 582, 1950

76. Zeegmuller E. Schwere Hautmuskelerkrankung unter dem Klinischen Erscheinungsbild einer Dermatomyositis mit Coxsackie Virusbefund Deutsche Med Wchnschr *78* 190, 1953

The Heart in the Connective Tissue Diseases

by Joseph T. Roberts

A GREAT CHANGE HAS EVOLVED in the past decade in appreciation of the frequency and significance of heart disease in patients with rheumatoid arthritis as well as the other connective tissue (collagen) disorders It is apparent that many, if not most, of the patients suffering from one of these maladies have severe changes in the heart which may require treatment during the course of the disease. The most common connective tissue disease with cardiac complications is rheumatic fever. Heart disease of some degree is evident at some period in almost all patients with this malady. The cardiovascular manifestations of rheumatic fever resembles those less well known in rheumatoid arthritis and the uncommon collagen diseases Distinction is often impossible except on the basis of arbitrary criteria or subsequent developments and specific studies

Until quite recently, it had been a common belief that heart disease was seldom caused by these common and uncommon collagen diseases with the exception of the syndrome known as Libman-Sachs disease, a manifestation of systemic lupus erythematosus, and one often masquerading as subacute bacterial endocarditis or non-specific myocarditis. So generally has this opinion been shared that the finding of myocardial, pericardial or valvular changes was often thought to be sufficient to distinguish patients with rheumatoid arthritis from those with rheumatic fever. It still is valid that in the early and acute phases of illness, it may be difficult to differentiate except in retrospect after the development of clearcut distinguishing peripheral or other lesions Another important concept in recent years has been the awareness that the heart may suffer from the effect of collagenous changes in peripheral organs or blood vessels of either the pulmonary or general system (table I). The converse relationship is also becoming more apparent with the realization that altered cardiac output or embolism arising from the heart in the connective tissue maladies may cause changes in peripheral tissues which in turn exaggerate the signs of the underlying heart disease. The treatment of heart failure, cardiac pain, arrhythmias and other cardiovascular problems is usually similar in patients with collagen system diseases and rheumatoid arthritis to that required in other etiological forms of heart disease.

TABLE I

CARDIAC CHANGES IN COLLAGEN DISEASES

(excluding Rheumatic Fever)

(Code. R—rare, O—occasional, C—common, U—usual, N—not related or not encountered, 1—early, 2—later)

MANIFESTATION	RA*	SLE*	PAN*	SD*	DM*	TTP*
Heart Failure	1 O			1 O		
	2 U	U	C		R	C
				2 U		
Heart Pain	C	C	U	1 R	R	R
				2 C		
Rate & Rhythm Changes	1—R	1 R	1 C	1 O		
					C	C
	2—C	2 U	2 U	2 U		
Enlarged Heart	C	C	U	R	O	C
Pericardial Effusion or Fibrin	C	C	U	C	O	C
Pericardial Constriction	C	C	C	C	O	N
Hypertension	1—C	1 R	1 C			
	2—O	2 C	2 U	O	O	R
Murmurs						
Systolic Mitral	U	U	U	U	O	C
Diastolic Mitral Rumble	C	U	C	C	O	R
Aortic Systolic	C	R	O	R	R	R
Aortic Diastolic	C	R	R	R	R	R
Pulmonic Systolic	C	C	C	U	C	O
Pulmonic Diastolic	R	R	R	R	R	O
Calcification of Pericardium	O	R	O	O	R	N
Fibrinoid Nodules in Pericardium	C or U	C	C	R	R	N
Fibrinoid Nodules in Myocardium	C	C	U	C	C	O
Fibrinoid Nodules in Endocardium	U	U	C	O	O	R
Non Nodular Fibrinoid and Fibrous Changes	U	C	U	C	O	R
Coronary Arteries						
Fibrinoid Thickening of Intima	C	C	C	C	C	C
Amyloidosis, Especially Intimal	C	O	C	N?	N?	N?
Elastic Weakening and Bulges	N, R	N, R	U	N	N	O
Perivascular Cuffing	C	U	U	R	C	C
Coronary Occlusion	C	R	C, U	O	O	O
Intimal Ulcer, Thrombosis	O	C or U	U	R	R	U
Interstitial Myocarditis	C	U	U	U	C	C
Subendocardial Fibrosis	R	N	N	C	C	N
Myocardial Fibrosis	C	O	O	U	U	O
Myocardial Fibers Atrophic	C	O	O	U	N	C
Myocardial Fibers Without Atrophy	O	U	U	O	U	O
Myocardial Fibers Vacuolated	O	O	O	O	C	U

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Heart Pain	C	C	U	1 R 2 C	R	R
Rate & Rhythm Changes	1—R 2—C	1-R 2 U	1 C 2 U	1 O 2 U	C	C
Enlarged Heart	C	C	U	R	O	C
Pericardial Effusion or Fibrin	C	C	U	C	O	C
Pericardial Constriction	C	C	C	C	O	N
Hypertension	1—C 2—O	1-R 2 C	1 C 2 U	O	O	R
Murmurs						
Systolic Mitral	U	U	U	U	O	C
Diastolic Mitral Rumble	C	U	C	C	O	R
Aortic Systolic	C	R	O	R	R	R
Aortic Diastolic	C	R	R	R	R	R
Pulmonic Systolic	C	C	C	U	C	O
Pulmonic Diastolic	R	R	R	R	R	O
Calcification of Pericardium	O	R	O	O	R	N
Fibrinoid Nodules in Pericardium	C or U	C	C	R	R	N
Fibrinoid Nodules in Myocardium	C	C	U	C	C	O
Fibrinoid Nodules in Endocardium	U	U	C	O	O	R
Non Nodular Fibrinoid and Fibrous Changes	U	C	U	C	O	R
Coronary Arteries						
Fibrinoid Thickening of Intima	C	C	C	C	C	C
Amyloidosis, Especially Intimal	C	O	C	N'	N'	N'
Elastic Weakening and Bulges	N, R	N, R	U	N	N	O
Perivascular Cuffing	C	U	U	R	C	C
Coronary Occlusion	C	R	C, U	O	O	O
Intimal Ulcer, Thrombosis	O	C or U	U	R	R	U
Interstitial Myocarditis	C	U	U	U	C	C
Subendocardial Fibrosis	R	N	N	C	C	N
Myocardial Fibrosis	C	O	O	U	U	O
Myocardial Fibers Atrophic	C	O	O	U	N	C
Myocardial Fibers Without Atrophy	O	U	U	O	U	O
Myocardial Fibers Vacuolated	O	O	O	O	C	U

Prognosis						
Decline in Decades	U	R	R	R	N	N
Death in 2 5 Years	O	U	U	C	R	N
Death in Months	R	C	C	U	C	C
Death in Weeks or Days	R	R	R	R	U	U
Invalidism, Cardiac	1—O	1-R	1 R	1 O	1 C	1-U
	2—U	2-U	2 U	2 U	2-C	2 U

*RA—Rheumatoid Arthritis, SLE—Systemic Lupus erythematosus, PAN—Polyarteritis; SD—Scleroderma, DM—Dermatomyositis, TTP—Thrombotic Thrombocytic Purpura

THE FIBROUS SKELETON OF THE HEART

The fibrous skeleton of the heart, as in other organs, consists of: (1) the three types of connective tissues fibers (collagen, elastic and reticular fibers); (2) specialized cells producing and holding these fibers in place, particularly the fibroblasts and migratory tissue cells; and (3) the material between the other elements which is referred to as the "ground substance" or "interstitial spaces and fluid." The *collagen* fibers are thick, long straight fibers with a relatively limited power of stretching and vary between 1 and 20 microns in diameter. These fibers occasionally may branch and fuse but usually are bound firmly at each end to give a point of fixation. The *elastic* fibers are much thinner, are highly refractile and appear as both single strands and as groups of strands, lamina or layers. They often appear to be unattached and are characterized by more elasticity. The *reticular* fibers are thin fibers arranged in loose, basket-like networks around other units of *structure and usually are not visible except with specialized methods of study.*

The large, strong, firm collagen fibers are arranged in the heart in the following several important structural units which have been specifically developed in nature to provide the heart with its essential units for operation. The *heart valves* (mitral, aortic, pulmonic and tricuspid) are peculiarly adapted shelves of dense collagen which extend into the blood stream with special attachments at the commissures, with nodules (of Arantius) and lunular edges molded so as to guide the flowing blood in one direction only *in a normal heart These shelves of collagen are poorly supplied with* blood or lymph vessels normally and are covered by two layers of endocardium. The mitral and tricuspid semilunar valves are scalloped at their edges with the points being continuous with dense cords of collagen (also surrounded by *endothelium) which are known as the chordae tendineae* These chordae tendineae in each ventricle appear to be attached to the papillary muscles but actually are continued directly into the *broad planes of interstitial collagenous tissue* lying between bundles of muscle fibers in the myocardium From these large *bands and planes of connective tissue, thinner planes of collagenous tissue* subdivide the myocardium into smaller compartments,

containing the units of heart muscle cells These subdividings become smaller until there are surrounding networks of collagen tissue about each strand of heart muscle syncitium The larger planes of interstitial tissue in the myocardium are fused with a very dense unit of collagenous fibers which forms the four *valvular rings* (aortic, mitral, pulmonary and tricuspid) Between these four adjacent rings of dense collagen, there are dense *triangles* of collagen which bind the rings together and give firm fixation for the other supporting tissue and contracting muscle of the heart and for the two major outflow tracts

In addition to these units of the fibrous skeleton of the heart, collagen and elastic fibers (and to a lesser degree reticular fibers) contribute to the *supporting wall of each of the blood and lymphatic vessels* throughout the heart. The connective tissue fibers are more abundant in the walls of the arteries and arterioles than in the veins, lymphatics and venules but even the capillaries appear to have at least one or two strands of collagenous fibers outside the endothelial lining Collagen fibers also surround, as a sheath, the clumps of specialized cells of the nodes and bundles in the conduction apparatus and in the ganglion cells and nerve supply of the heart. In some hearts, a specialized space known as "the sheath of Curran" may be demonstrated as a fascial bursa surrounding the atrioventricular bundle of Kent and His A loose plexus of connective tissue, chiefly collagen, is present in the subendocardial layer between the endothelial lining of the heart's chambers and the myocardium. A similar layer is found between the myocardium and the visceral pericardium or epicardium In this important subepicardial sheath are found the superficial cardiac vessels and lymphatics The parietal pericardium is also a dense sheath of collagen with a thin outer sheath loosely blending with the surrounding tissues, specially modified to prevent the heart from expanding too greatly during diastole and to give some fixation to surrounding structures The pericardium also allows the heart to swing suspended within the rigid bony thorax, as does a body in a hammock, with flexible support but also protection against shock by resilience during motion or blows Diseases of the collagen and fibrous tissue in any portion of the heart or its vessels may interfere with the functions of these fibrous parts of the heart or of the other functional units of the organ supported by them

RHEUMATOID ARTHRITIS

Clinical Changes

Until recent years, it had been a general belief that heart disease occurring in patients with rheumatoid arthritis was coincidental, with no causal relation and furthermore that such associations were quite rare In the past ten years, however, a highly controversial literature from many areas has

reflected what now seems to be a fairly common association. The incidence of moderate to serious degrees of heart disease in patients with rheumatoid arthritis is reported variously as between 10 per cent and 50 per cent. This wide range reflects chiefly a variation in the criteria used for diagnosis of the heart disease, the severity of the rheumatoid arthritis as well as the period and intensity of observation of patients under study. My own experience indicates that the great majority of patients with rheumatoid arthritis, in a clinically typical form, will have recognizable to severe signs of heart disease during the acute period of the disease and certainly during the later or near-terminal phases.

During acute phases of rheumatoid arthritis, especially during periods with fever or if exertion is strenuous, shortness of breath, severe palpitation, rapid heart rate with rapid shallow respiration and cough, with cyanosis (often mottled) and precordial, substernal or even shoulder and arm pain, may be found. Irregularities or slowing of the pulse are found also. Frequently, pain in the chest, arms or neck in arthritic patients is attributed to dysfunction in the neuromuscular or skeletal supportive tissue. In addition to such mechanisms, these changes may be caused by referred cardiac pain of the anginal or coronary insufficiency types. It has not been unusual to have the pain persist long enough to be suggestive of acute myocardial infarction. This indeed occurs on the basis of either the intrinsic changes by the disease in the coronary vessels or secondary to the ordinary type of coronary artery disease aggravated by the anemia, tachycardia and toxemia of rheumatoid activity. This association of coronary disease and rheumatoid arthritis is more than that due to age, weight, habits and other known factors which may modify coronary disease. Abrupt increase in weight may occur due to edema of the lower extremities, fluid retention in the abdomen or chest caused by heart failure and by hepatic, renal, dietary or other factors. Of these, salt retention and dietary use of excessive fat and calories are significant.

Rheumatoid arthritis may make its appearance initially in people who are moderately or seriously overweight and this more than anything else predisposes to the onset of signs of heart failure or cardiac insufficiency. In later phases, of course, rheumatoid arthritis patients may be underweight and malnourished with signs of nutritional deficiencies confusing and altering the picture of the heart disease. A deep-seated, dull aching pain around the heart may be revealed if carefully elicited and is related to pericarditis during acute periods of activity as well as the obliterative or constrictive pericarditis sometimes recognized during the late phases of rheumatoid arthritis. Palpitation, cardiac fear, cardiac neurosis, apprehension and the sense of impending disaster are noted also. Systolic mitral murmurs of grade I or II

intensity may be present with exaggeration to grade III or IV on exertion. Systolic pulmonary murmurs are next in frequency and the two are often associated or interchanged. Diastolic mitral murmurs or even presystolic apical rumbles, highly localized and identical with those of rheumatic mitral stenosis usually are transitory during the acute phases of the disease with associated enlargement and cardiac dilatation These murmurs are often out of proportion to valvular findings during autopsy They may be due to valvular thickening, shortening or adhesions, or to myocardial dilatation, anemia, beriberi or other metabolic changes Pulmonary diastolic or aortic diastolic and systolic murmurs are observed less commonly although in the older age group of patients a harsh, intense aortic systolic murmur transmitted into the neck is not unusual because of either coincidental or possibly related aortic stenosis.

Pericardial friction rubs (usually of fleeting, recurrent and indistinct type) have been reported in rheumatoid arthritis as well as gallop rhythm of either systolic or diastolic type, splitting of either first or second sounds or both, exaggeration of mitral first sounds or pulmonic second sounds or other changes in the heart tones are common and especially exaggerated by effort. During clinically active phases or after the prolonged inactivity, the heart tones are of poor quality, low intensity and at times inaudible Petechiae, ecchymoses, easy bruising, enlargement of the spleen and liver, coughing up blood or other sputum and peripheral or central thrombo-embolic phenomena are often the terminal manifestations or may appear cyclically after apparent improvement from an acute arthritic phase.

Ballistocardiograms and other methods may reflect the myocardial, valvular, pericardial or coronary arterial abnormalities None of these physiological variations has specific relation to etiological factors; they indicate anatomical and functional changes in basic mechanisms The more nearly routine use of the electrocardiogram, roentgenogram and biochemical studies, especially of the electrolytes, has been most helpful in the recognition of the frequency of cardiac involvement by rheumatoid arthritis The electrocardiographic findings include variable and shifting changes in the T-waves and S-T segments Atrial tachycardia, multifocal premature systoles (atrial or ventricular), wandering pacemaker, severe sinus arrhythmia, abnormal U-waves, prolonged or shortened QT and PR segments are seen at times Atrial fibrillation and flutter, low voltages and ventricular tachycardia usually indicate critically serious myocarditis or pericarditis and, of course, ventricular fibrillation or cardiac standstill are most ominous signs

Pathological Changes

There are wide variations in the pathological signs of involvement of this

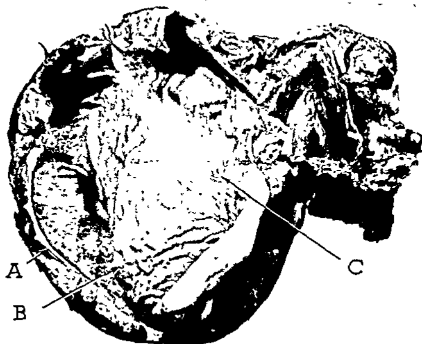


FIG 1 Chronic nodular pericarditis in a case of rheumatoid arthritis. The parietal pericardium is thick and distended, the visceral pericardium is thickened, wrinkled and studded with small nodules A few fibrous adhesions are seen in the left upper area of the picture The distended pericardial cavity was filled with yellowish turbid material A. Parietal pericardium B Visceral pericardium C Nodules in pericardium

organ because of (1) the large number of collagen fibrous units in the heart and its appendages; and (2) the great variation in changes in these collagen fibers by the various stages of activity of the disease and modification by varied forms of treatment. In the bands of collagen fibers found throughout the myocardium as well as in the pericardium and endocardium, there are two principle forms of alteration: (1) a nodular form (fig 1) with nodules resembling the nodules found under the skin and near the tendons, varying in size from less than one mm. to one cm occasionally, and consisting of irregular whorls of collagen fibers with accumulations of large amounts of brightly eosinophilic fibrinoid material or ground substance, and fragmented collagenous fibers (fig. 2); and (2) a non-nodular form with irregular thickening, fibrinoid changes, irregular staining characteristics, thickening and fragmentation of the collagenous fibers throughout the heart. Either type of change may be found in relation to the walls of the coronary arteries or arterioles (fig. 3) and in the walls of the aorta, pulmonary artery or attached veins.

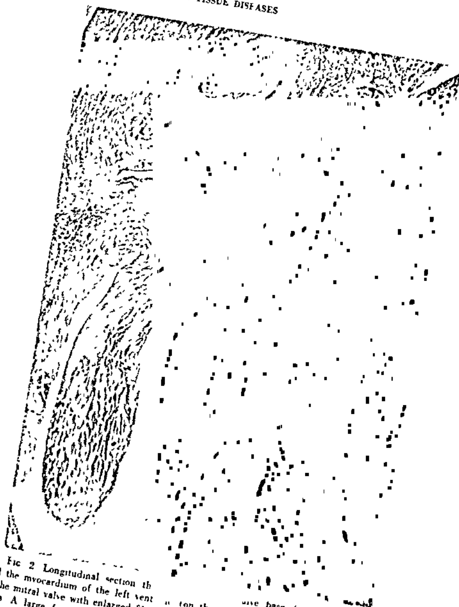


Fig 2 Longitudinal section th[illegible] ...ve base (at left of picture) and the myocardium of the left vent[illegible] (on the right) Note thickening of the base of the mitral valve with enlarged fibrinoid collagen fibers with areas of cellular infiltrations A large frond like, non bacterial vegetation is seen on the myocardial surface of the mitral valve, above which are three smaller protrusions In these vegetations are areas of fibrinoid degeneration with deeply eosinophilic strands of fibrinoid material especially in the vegetation and in the angle between the valve and myocardium Magnification x50

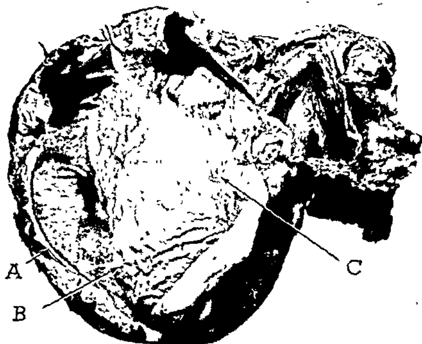


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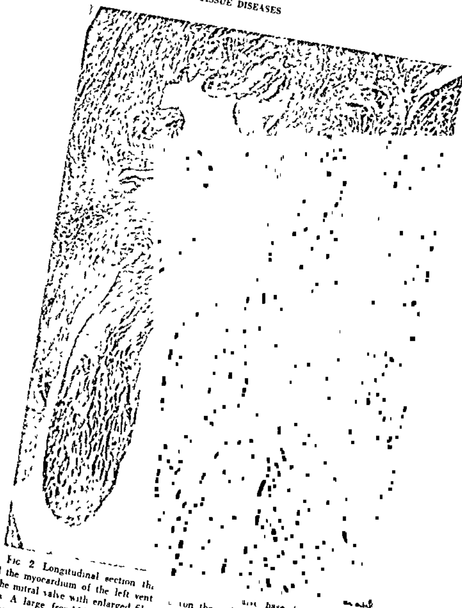


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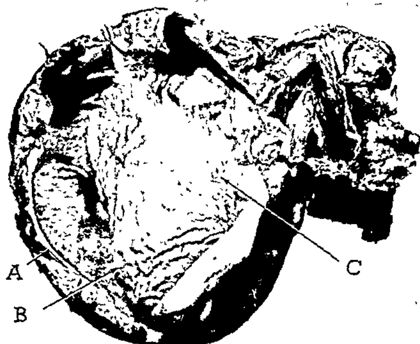


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Valvular and endocardial lesions, in association with rheumatoid arthritis, have been the point of most argument as to significance Opacity and nodular or plaquelike thickening of the endocardium at the edges of the mitral or other valves, similar lesions or with small granular nodules or granulomas on the chordae tendineae or on the endocardium lining the cavity of the left ventricle (more than other chambers) have been reported. These changes have been thought to be due to (1) the disease, or (2) to coincidental associations of non-specific or aging factors, or (3) the residuals of unrecorded rheumatic fever. Because of a recognition in recent years of the fact that rheumatoid arthritis may be a forerunner of one of the uncommon collagen diseases, the findings in autopsies today of rheumatoid arthritis may be even more bizarre and complicated than in the past. Whether such a changing trend is simply coincidental or is due to the effect of more common use today of the host of available potent drugs and hormones, to complicating infections and metabolic changes, or to other factors, cannot be determined with certainty at this time. Changes in the aortic valve, especially aortic valvular stenosis, have been recognized in the past but were thought to be due to coincidence However, in some cases, nodules of a more specific type and resembling those of rheumatoid arthritis in other parts of the body have been found in the aortic valve of cases with either severe aortic stenosis or aortic regurgitation or a combination of the two functional disorders.

SPONDYLITIS, MARIE-STRUMPELL DISEASE, OSTEOPOROSIS, FELTY'S SYNDROME, PALINDROMIC ARTHRITIS, AND STILL'S DISEASE

In each of these conditions, the occurrence of heart disease is less frequent than in the typical forms of rheumatoid arthritis Any of the comments made in the previous section on rheumatoid arthritis may be appropriate at times in discussion of these conditions which are considered by some clinicians to be subdivisions or variants of the broad spectrum classified as rheumatoid arthritis Minor variations in emphasis are noted With rheumatoid spondylitis or Marie-Strumpell disease, the heart may be affected as manifest by (1) cor pulmonale and by limitation of the vital capacity due to the fixation of the ribs on the sternum and spinal column, or (2) aortic insufficiency or stenosis. In Still's disease or Felty's syndrome the heart is less often involved than in typical rheumatoid arthritis and is more likely to be affected by secondary changes in the coronary arteries, nutrition, blood pressure, anemia, leukopenia with susceptibility to infections, polycythemia and other associated factors than by rheumatoid arthritis itself

In an analysis of various reports of rheumatoid arthritis, the frequency of amyloidosis varies from "rare" to as high a frequency as one of six patients or one of eleven patients studied at autopsy. Amyloidosis may be responsible for the high frequency of albuminuria in severe rheumatoid arthritis, and it may be aggravated by use of cortisone or related materials. Emaciation is an important and outstanding finding, at times with atrophy of the heart but more frequently with cardiac enlargement, hypertrophy and congestion of organs as in congestive heart failure from other causes. The incidence of pericarditis is noteworthy. Complete obliteration of the pericardial cavity with thickening of both layers of the parietal and visceral pericardium or epicardium has been an unexpected finding at autopsy in patients with rheumatoid arthritis (fig. 4). Usually there has been relatively little gross evidence of severe constriction of the heart although the peripheral edema and cardiac type of disability in retrospect might have suggested this at times. The pericardial changes have not been of the obliterative type but have comprised fibrinous exudates, excess amount of effusion, or nodules resembling those found under the skin. In rare cases the pericardial sac contains an accumulation of thick creamy or yellow material high in cholesterol

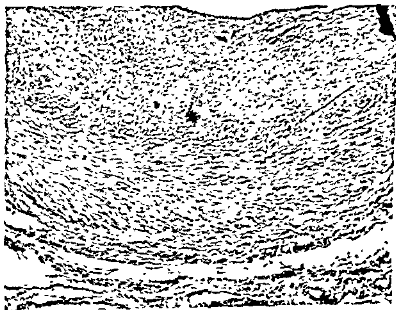


FIG. 3 Wall of a coronary artery in rheumatoid arthritis, from the heart shown in *Figure 1* Severe fibrinoid accumulations and degeneration of the subendothelial and medial layer are evident with infiltration by lymphocytes and other cells in the adventitia Magnification, x120 Arrow indicates internal elastic lamina between thick fibrinoid of intima and the media

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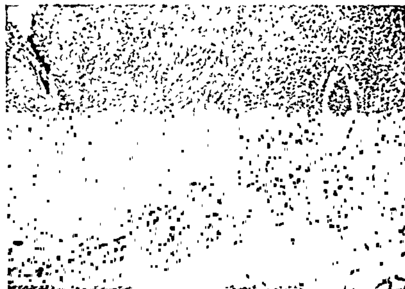
SYSTEMIC LUPUS ERYTHEMATOSUS

Involvement of the heart has been recognized in systemic lupus erythematosus more often than in the other uncommon collagen diseases. Recognition of the L. E. cell has brought new emphasis upon the malady, especially in young adults with arthritis or arthralgia. In my experience, it has not been unusual to encounter patients with a diagnosis of acute rheumatic fever or rheumatoid arthritis for a period of time and subsequent development of the diagnostic features of systemic lupus. In other instances, the incidental



4 a

FIG 4. Nodular areas of visceral pericardium with underlying myocardium and coronary artery from the heart in figure 1. (a) Magnification. x25 (b) x152



4 b

study of a muscle biopsy, or a smear for L.E cells, the finding of leukopenia, an abnormal serum globulin or eosinophilia leads to the correct diagnosis

Clinical Features

In the past, systemic lupus has been considered to be a disease principally of females After an initial transient illness with low-grade fever and joint pains with swelling and tenderness and a blowing systolic mitral murmur, the patient responds to symptomatic treatment with little evidence of serious involvement of vital structures Several months or years later, however, there is recurrence of symptoms overshadowing the arthralgia Moderate to severe anemia, albumin and occasional red cells in the urine, with pallor and tenderness over the liver and spleen may then be found As the severity of systemic lupus varies with apparently spontaneous remissions, often for months or even years, so does the severity of heart disease vary In almost every fashion, it resembles the heart disease of rheumatic fever and the less well recognized heart disease of rheumatoid arthritis In many cases, the disease progresses to generalized involvement with uremia, convulsions, severe anemia, heart failure, embolisms, thrombotic complications, septic fever, coma and death In other patients, however, there are relatively brief episodes of sudden anemia, requiring transfusion or spontaneously remitting, with fever, fatigue, arthralgia and flaring of the skin rash During such phases, there may be a rapid heart rate with sinus or atrial tachycardia, atrial fibril-

lation or flutter, sinus arrhythmia, weakening of the heart tones and shortness of breath or moderate edema. A pericardial friction rub and variable murmurs are often heard during this phase. These murmurs may be either diastolic or systolic but usually are widespread systolic precordial murmurs The presence of rales, enlargement and tenderness of the liver, puffiness of the face and edema indicates congestive heart failure Glomerulonephritis may be suspected as the cause. The electrocardiogram is often confirmatory of these changes and usually shows non-specific RST segment and T wave changes typical of a non-specific type of myocarditis and pericarditis. The blood pressure in this phase is usually normal unless it is decreased below normal by the presence of pericardial effusion and tamponade or the heart failure of myocarditis. Occasionally the blood pressure is elevated through the illness but if elevated in the early phases, it is usually only moderately so and transient. Gallop rhythm, an accentuated pulmonary second sound, loud and accentuated or reduplicated mitral first sound or other changes in the cardiac tones may reflect the widespread and variable damage to the heart muscle and valves. During the periods of remission, each of these abnormalities may disappear. After intervals of relative good health, longer periods of illness are mixed with shorter periods of convalescence until the terminal phase begins. Deterioration may be apparent with rising blood pressure, persistent albuminuria and hematuria with casts and poor concentrating ability, severe and relatively intractable congestive heart failure of both the pulmonary and peripheral systems, thrombo-embolic complications of small vessels throughout the body and occlusion of vessels to vital structures. In this phase, the heart may be enlarged.

Pathologic Findings

Classically, the characteristic lesion of the heart is the "non-bacterial or sterile verrucous endocarditis" of Libman and Sacks These are slightly elevated, flattened plaques or nodules most abundant on the ventricular surface of the mitral valve although observed elsewhere on any of the valves, chordae tendineae or endocardium of the chambers. Microscopically, these are thickened accumulations of eosinophilic collagenous fibers with areas of fibrinoid degeneration and invasion by lymphocytes and covered with layers of thrombosis at times but without colonies of bacteria unless this is a secondary complication (fig 5). The heart may be moderately enlarged with hypertrophy and dilatation; pale and altered staining characteristics of the muscle fibers may be demonstrated. The pericardium, myocardium and endocardium show ecchymoses, small pinhead scars and accumulations of inflammatory cells about the walls of the small blood vessels with thickening of the media and intima and thrombosis (fig. 6). At times these lesions are difficult to distinguish from Aschoff bodies, zones of non-specific myo-

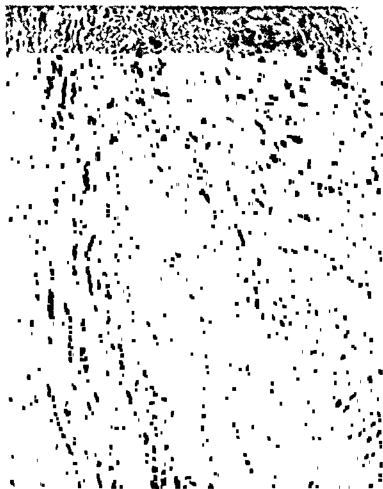


FIG 5 Fibrinoid material in the angle between the valve and the ventricular wall of a case of systemic lupus Magnification x160

carditis or the lesions of rheumatoid arthritis, scleroderma or polyarteritis Fibrinous pericarditis is observed upon pathological examination in a number of the patients. A large pericardial effusion, usually serous but sometimes bloody, has been reported There are few diagnostic features in the pericardial or myocardial abnormalities of lupus but today the disease should be suspected in patients in whom these abnormalities are found. Hypertrophy of the heart may be concentric, involving both ventricles or may involve

either ventricle more than the other. In such a case, the electrical axis may rotate, to the left if the left ventricle is enlarged as with severe hypertension, or to the right and vertically if the right ventricle is enlarged as a sequel to the commonly associated pulmonary fibrosis of systemic lupus erythematosus

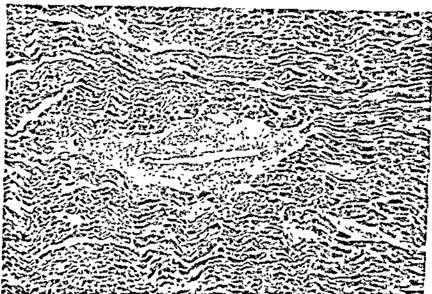


FIG 6. Arterioles in the myocardium of a case of lupus The narrowed lumen (due to fibrinoid thickening of the intima) with eccentric perivascular cellular infiltration is typical of changes found in arterioles throughout the entire body Magnification· x72

POLYARTERITIS

Polyarteritis or polyangiitis, is a disease with complicated clinical manifestations related to the widespread and variable inflammatory changes to be found in the walls of small blood vessels of all types and in all areas The diagnostic lesion is a fibrinoid degeneration of the collagen fibers in the medium sized and small blood vessels, arterial, arteriolar, and venous throughout the body Often these changes lead to weakening of the wall of the vessel with nodular bulging and accumulation of inflammatory cells nearby, which when present, gives rise to the nodules from which the older name "periarteritis nodosa" was derived (fig. 7). In the majority of situations, however, the nodules are absent or of minor importance. Since the early description of the disease by Kussmaul and Maier in 1866, polyarteritis has been considered to be extremely rare until the past ten years As with the other collagen disorders, however, its frequency has become more common or its recognition has become more widespread with better understand-

ing of the diagnosis. Although the disease may involve many organs, the kidney is affected more frequently than any other organ, with the heart second in frequency. It is obvious that a number of patients with polyarteritis will show signs suggestive of heart disease at some phase, due either to the involvement of the heart itself or of one of the other organs which predispose to heart failure.



Fig 7 Drawing of the heart of a patient who died from polyarteritis The mulberry-like aneurysms of the coronary arteries with pericardial changes are noted

The onset is usually insidious and progressive, less often intermittent, but may be sudden and rapidly terminal if major arteries with thrombosis or hemorrhage from ruptured small aneurysms in vital areas are involved. Because the disease involves principally the middle and small sized arteries and arterioles, the clinical manifestations vary greatly according to the organ affected. Polyarteritis produces cardiovascular symptoms and signs due to gross and microscopic involvement of any portion of the heart As a result, tachycardia, rhythm disturbances, progressive hypertension and changing murmurs with friction rubs are common. During acute, progressive or terminal phases, however, more so than in the other collagen disorders, primary involvement of the arteries leads to occlusion of coronary and

renal vessels with the typical signs of either myocardial infarction or hypertension, with related pericarditis, congestive heart failure and thromboembolic complications. With these distinctions, the findings on physical examination, electrocardiographic and other studies, may be those of the other collagen diseases. There may be any degree of cardiac enlargement, myocarditic bulging, valvular or functional murmurs, rhythmic changes in the ECG or pericardial involvement.



FIG 8 Polyarteritis of a coronary arteriole in the myocardium. The severe eccentric perivascular infiltration with round cells and other inflammatory cells plus fibrinoid changes in all three layers of the arteriolar wall are evident Ulceration and loss of the elastic lamina and of the intima is associated with weakening and bulging of the arteriolar lumen and wall Magnification x521. Reproduced by permission of the Armed Forces Institute of Pathology, Walter Reed Army Medical Center, Washington 25, D C, picture number 54 19229 Courtesy of Dr W B Manion

PATHOLOGIC FINDINGS

Microscopically, the lesion of polyarteritis is segmental with injured areas merging into normal lengths. In the acute phase necrosis and thickening of the collagen fibers is most severe in the media and less so in the intima and adventitia of the small arteries The thickened collagenous fibers undergo fibrinoid degeneration. Inflammatory cells, especially eosinophils, infiltrate the vessel walls. Initially, the media and adventitia are damaged more than the intima. Usually this leads to thickening of the wall which is eccentric and extends into the surrounding periadventitial tissue. Commonly in later phases, rupture of the internal elastic lamina allows the effect of the



Fig 9 Myocardial fibrosis with atrophy of muscle cells and proliferation of dense collagenous fibers in the heart of a patient dying from scleroderma A few cellular infiltrations are seen Magnification x140 Reproduced by permission of the Armed Forces Institute of Pathology, Washington, D C. Picture number 54 18881

blood, pounding under pressure, to herniate the wall so that aneurysmal bulging of the vessel occurs in a nodular fashion along its course. Ulceration of the intima is more common than proliferation and thrombosis with partial or complete occlusion usually follows (fig. 8).

In some cases, apparent efforts at healing occur with fibrosis and atrophy of the vessel and infarction of the area supplied unless collateral circulation develops. In some patients, the polyarteritis may be confined to only a single vessel such as one coronary artery or one vessel in a brain or in the kidney. In the majority of patients, however, the disease progresses after the clinically recognized onset This is especially true in patients with cardiac involvement. A striking and diagnostic gross finding is the presence of nodular or aneurysmal bulging of the coronary arteries, often throughout their entire length Obliterative or other forms of pericarditis, sclerotic or valvular changes, focal myocarditis due to occlusion or perivascular inflammation in small coronary vessels have been reported. The heart may be moderately enlarged (500-600 Gm in weight) rather than the cor bovinum (700-1000 Gm) variety unless hypertension has been severe for a long time. Myocardial infarction of segmental, diffuse and patchy, recurrent, or aneurysmal forms may be a basis for surprise when infarction is recognized in a relatively young person Such a wide spectrum of anatomical changes explains the variability of electrocardiographic or roentgenographic signs.

Involvement of the heart (fig. 9) is one of the ments during scleroderma. The patient may seek med of cardiovascular symptoms or signs with severe and graphic abnormalities. At other times, the diagnosis is major complaints referable to the small blood vessels o The skin on these areas, especially of the phalangeal sha contracted, non-elastic, shiny and relatively poor in sens patients described the appearance of his fingers as "like th glazed ceramics", and at other times as waxy, cadaveric or

Cyanosis with reticular striping, patchy areas of re at the fingertips, loss of nails and hair on the hands or fing bility of the skin in the involved areas lead to uselessness parts. A pericardial friction rub may be detected. The heart small or contracted on study by radiography. Various murm reported from time to time. Murmurs are suggestive of mitra or of mitral stenosis during the intermediate phase of the dise trocardiogram reflects the widespread myocardial damage wit variable changes in the ST segment. T wave contour of all waves of bundle branch block, atrioventricular conduction defects a disturbances of all types Masking these changes or obscured by be found either (1) the left ventricular hypertrophy, strain and nance due to the mitral insufficiency or hypertension commonly by the disease, or (2) the right ventricular hypertrophy, strain an derance with atrial injury and changes which develop as a seque pulmonary fibrosis of scleroderma.

The changes in scleroderma are most severe in the myocardiu collagen fibers are thickened and proliferated in both the large and fibrous bands throughout the muscle. Frequently, myocardial scarr of an unusual type. The scars are unusually vascular at times and resemble granulation tissue more than do the scars resulting from ar sclerosis or an old myocardial infarction. In other areas the muscle fi appear atrophied, fractured and very small. Many fibers appear disi grated or lost. They resemble the small fibers reported by Roberts and B in their experimental and clinical study of constrictive pericarditis whi suggested the term "atrophy of disuse". It is unusual to find cellular infiltr tions except for small numbers of eosinophils in the fibrous tissue. Peri cardial involvement is often reported but usually less constricted or thick ened than in other causes. Subendocardial fibrosis is common as an exag geration of the myocardial fibrosis. Thickening of the connective tissues in the intima seems to occur earlier than the proliferation of collagen of fibrinoid type in the media and adventitia. Valvular changes are less severe

than those in the myocardium, endocardium of the cavities and pericardium although all types of valvular changes have been reported. Thrombi within the cavities, which may give rise to embolism elsewhere, are not infrequent



FIG 10 Myocardial fibrosis in a case of dermatomyositis (without the severe atrophy of heart muscle cells typical of scleroderma) Fragmentation of the muscle cells, thickening and edema of the interstitial connective tissue and cellular infiltrations in the myocardium are illustrated Magnification x140 Reproduced by permission of the Armed Forces Institute of Pathology, Washington, D C Picture number 54-18861

DERMATOMYOSITIS

This, the last of the generally recognized uncommon forms of collagen diseases, is less well identified clinically and anatomically than the ones discussed previously Its characteristics may overlap those of some of the other collagen disorders which are better known As suggested by its name, dermatomyositis, involves the skin and the muscles throughout the body Arthralgia and generalized or migratory articular symptoms may occur with dermatomyositis but are secondary to injury to the collagen tissue in the skin and in the muscles Involvement of the cardiovascular system, as in the other collagen disorders, may include tachycardia, irregularity of the heart action, conduction defects and evidence of coronary insufficiency such as angina pectoris or congestive heart failure Microscopically (fig. 10) the collagen fibers of the involved areas of the skin, muscles and the viscera including the heart, are thickened, apparently proliferated or increased in number, with these two *identifying features (1) apparent increase of* interstitial matrix or edematous material of fibrinoid nature between the

collagen fibers and (2) abundant infiltration with accumulations of lymphocytes in this interstitial material, especially between the muscle fibers and surrounding the blood vessels, often with a few monocytes and occasional polymorphonuclear leukocytes with *fibroblasts, proliferating capillaries and* debris from deteriorated muscular fibers. In other areas, minimal degeneration of muscle fibers with increased fibrous connective tissue is found throughout the myocardium and in other areas. Grossly, the myocardium may appear to be more dense without a great increase in volume. The color may resemble hypertrophy. Pericarditis and endocarditis are less prominent than with the other collagen disorders. The fibrous areas in the muscles of the heart and skeletal system appear "caked" *due to swollen collagenous* fibers which are highly refractile microscopically.

Bibliography

Asboe Hansen, G. (editor) Connective Tissue in Health and Disease. Copenhagen, Ejnor Munksgaard, 1954

Baehr, G, Klemperer, P and Schifrin, A A diffuse disease of the peripheral circulation (usually associated with lupus erythematosus and endocarditis). Tr A. Am Physicians *50* 139, 1935

Baehr, G, Klemperer, P and Schifrin, A · An acute febrile anemia and thrombocytopenic purpura with diffuse platelet thrombosis of capillaries and arterioles Tr. A Am Physicians *51* 43, 1936

Baggenstoss, A H and Rosenberg, E F Cardiac lesions associated with chronic infectious arthritis Arch Int Med *67* 241, 1941

Baggenstoss, A H. and Rosenberg, E F Unusual cardiac lesions associated with chronic multiple rheumatoid arthritis Arch Path *37* 54, 1944

Ball, J. Rheumatoid arthritis and polyarteritis nodosa Ann Rheum Dis *13*, 277, 1954

Bayles, T B. Rheumatoid arthritis and rheumatic heart disease in autopsied cases Am J. M Sc *205* 42, 1934

Bevans, M, Nodell, J, Demartius, F and Ragan, C. Systemic lesions of malignant rheumatoid arthritis Am J Med *16* 197, 1954

Bradfield, J Y and Hejtmancik, M R Cardiac disease and rheumatoid arthritis. *Arch Int Med 86 1, 1950*

Bunim, J J, Sokoloff, L, Williams, R R and Black, R L Rheumatoid arthritis. Recent advances in our knowledge concerning pathology, diagnosis and treatment (a review) J Chron Dis *1* 168, 1955

Davis, R L, Brunson, J. G and Fehr, P E.: Cardiac fibrinoid lesions produced by cross circulation or temporary A V shunts Circulation *5* 11, 1957.

East, T. and Oram, S The heart in scleroderma Brit. Heart J *9*: 167, 1947

Ehrenreich, T and Olmstead, E V. Malignant hypertension following administration of cortisone in periarteritis nodosa *Arch Path 52* 145, 1951.

Ellman, P Scleroderma with hypertension Proc Roy. Soc Med *31 869, 1938*

Feiring, W.. Incidence of carditis in rheumatoid arthritis New York J. Med *45*, 1855, 1945.

Fernando, P B and Wijenaike, W.: Rheumatoid arthritis and heart lesions Indian Heart J *5*: 187, 1953

Fingerman, D L and Andrus, F. C Visceral lesions associated with rheumatoid arthritis Ann Rheum Dis 3 168, 1943
Fischmann, E J and Gwynne, F J The heart in rheumatoid arthritis Brit Heart J 10 125 1948
Friedberg, C. K and Gross, L. Non bacterial thrombotic endocarditis associated with acute thrombocytopenic purpura Arch Int Med 58 641, 1936
Friedberg, C K, Gross, L. and Wallach, K Non bacterial thrombotic endocarditis associated with prolonged fever, arthritis, inflammation of serous membranes and widespread vascular lesions Arch Int Med 58 662, 1936
Goldman, I R, Young, J M and Knox, F H Myocardial involvement in generalized scleroderma Dis Chest 25 94, 1954
Gould, S E Pathology of the Heart Springfield, Thomas, 1953
Griffith, G C and Vural, I L Polyarteritis nodosa, a correlation of clinical and post mortem findings in seventeen cases Circulation 3 481, 1951
Gross, L The heart in atypical verrucous endocarditis (Libman Sacks) Contributions to the Medical Sciences in honor of Dr Emanuel Libman by his pupils, friends and colleagues New York, The International Press, 1932
Gross, L. Cardiac lesions in Libman-Sacks disease with consideration of its relationship to acute diffuse lupus erythematosus Am J Path 16 375, 1940
Heptinstall, R H and Sowry, G S C Peripheral neuritis in systemic lupus erythematosus. Brit M J 1 525, 1952
Humphreys, E M The cardiac lesions of acute disseminated lupus erythematosus. Ann Int Med 28 12, 1948
Israel, H L. The pulmonary manifestations of disseminated lupus erythematosus Am J M Sc 226 387, 1953
Kahlmeter, G De l'existence de lesions myocardiques et valvulaires dans les diverses formes de polyarthrities chroniques et des conclusions qu'on en peut tirer touchant l'etiologie et le groupement clinique des polyarthrities chroniques Acta med Scandinav Supp 59 611, 1934
Kampmeier, R H Vascular disease due to hypersensitivity, so-called diffuse collagen disease Am Pract & Digest Treat 1 113, 1950
Kellogg, F and Cunha, F Dermatomyositis, report of a case associated with rheumatic heart disease California & Western Med 50 337, 1939
Kinney, T D and Maher, M M Dermatomyositis—a study of five cases Am J Path 16 561, 1946
Klemperer, P, Pollack, A D and Baehr, G Pathology of disseminated lupus erythematosus Arch Path 32 569, 1941
Libman, E. and Sacks, B A hitherto undescribed form of valvular and mural endocarditis Arch Int Med 33 701, 1924
Liebow, I M, and Feil, H The electrocardiogram in lupus erythematosus disseminatus. Am. J Med., 3 41, 1947
Lloyd, W E and Tonkin, R D Pulmonary fibrosis in generalized scleroderma, review of the literature and report of four further cases Thorax 3 241, 1948
Middleton, W S and McCarter, J S The diagnosis of periarteritis nodosa Am J M Sc 190 291 1935
Mustakallio, K K and Sarajas, H S S Some aspects of scleroderma heart disease Am Heart J 47 437, 1954
Pirani, C. L. and Bennett, G A Rheumatoid arthritis A report of three cases progressing from childhood and emphasizing certain systemic manifestations Bull Hosp Joint Dis 12 335, 1951
Ragan, C. (editor) Transactions of the Second Conf on Connective Tissues, 1951,

New York: Third Conf., 1952; Fourth Conf, 1953, Princeton, New Jersey and Fifth Conf, 1954 Sponsored by the Josiah Macy, Jr Found, New York
Rakov, H L. and Taylor, J S Acute disseminated lupus erythematosus, atypical verrucous endocarditis, fever of unknown undescribed pulmonary lesions Arch Int Med *70* 88, *1942*
Reifenstein, E C, Reifenstein, E C, Jr and Reifenstein, G. H.: A variable symptom complex of undetermined etiology with fatal termination, including conditions described as visceral erythema group (Osler), disseminated lupus erythematosus, atypical verrucous endocarditis, fewer of unknown origin (Christian) and diffuse peripheral vascular disease (Baehr and others), Arch Int Med *63*: 553, 1939.
Richter, R B Peripheral neuropathy and connective tissue disease J Neuropath & Exper Neurol *13* 169, 1954
Roberts, J. T The effect of occlusive arterial diseases of the extremities on the blood supply of nerves Experimental and clinical studies on the role of the vasa nervorum Am Heart J *35* 369, 1948
Roberts, J T. Dynamics and circulation of heart muscle; cardiac reserve, heart pain, the cardiac cycle *In* Pathological Physiology and Mechanisms of Disease, William A Sodeman Philadelphia, Saunders, 1956
Roberts, J T and Beck, C S The muscle fiber size in constrictive pericarditis Am Heart J *35* 1, 1948
Roberts, J T, Murdock, H R, Jr, Campo, J L., Tanner, C J. and Paparella, J A: Blood vessels of nerves, as seen in living animals with quartz rod illumination Fed Proc 9 No 1, 1950
Rosenberg, E. F., Bishop, L. F., Hench, P S and Weintraub, H: Cardiac lesions in rheumatic arthritis Arch Int Med *85* 751, 1950.
Rosenberg, E F, Baggenstoss, A H and Hench, P. S., The causes of death in 30 cases of rheumatoid arthritis Ann Int Med *20* 903, 1944
Sinclair, R J G and Cruickshank, B A clinical and pathological study of sixteen *cases of rheumatoid arthritis with external nodular involvement (rheumatoid disease)* Quart J Med *25* 313, 1956.
Sokoloff, L The heart in rheumatoid arthritis Am. Heart J *45* 635, 1953
Steele, C W, Cardiac lesions in rheumatoid arthritis, J. Maine M. A *44* 308, 1953
Stryker, W A Coronary occlusive disease in infants and children Am J. Dis Child *71* *280*, *1946*
Symmers, W St C: Necrotizing pulmonary arteriopathy associated with pulmonary hypertension J Clin Path *5* 36, 1952
Sweeney, A R, Jr. and Baggenstoss, A H: Pulmonary lesions of periarteritis nodosa Proc Staff Meet., Mayo Clin *24* 35, 1949
Sussman, I and Price, P Right-sided endocarditis on a patent foramen ovale associated with periarteritis nodosa Ann Int Med *37*: 612, 1952
Talbott, J H and Ferrandis, R M Collagen Diseases New York, Grune & Stratton, 1956
Traut, E F.: Rheumatic Diseases—Diagnosis and Treatment St. Louis, Mosby, 1952
Tumulty, P A The clinical course of systemic lupus erythematosus J A M A *156* 947, 1954
Weiss, S, Stead, E. A, Warren, J V and Bailey, O T.: Scleroderma heart disease with a consideration of certain other visceral manifestations of scleroderma Arch Int Med *71* 749, 1953
Wilens, S L *and Glynn, J Hypertensive and non-hypertensive* periarteritis nodosa Arch Int Med *88*. 51, 1951
Young, D and Schwedel, J B The heart in rheumatoid arthritis; study of 38 autopsy cases. Am. Heart J. *28*. 1, 1944

Arthropathy in the Unusual Connective Tissu (Collagen) Diseases

by Salvatore R. La Tona

THE FREQUENCY WITH WHICH the usual connective tissue diseases are fir diagnosed as "arthritis" prompts us to evaluate the significance of joi manifestations in this group of maladies. Various writers, including Lem wand,[25] Haserick,[14] and Harvey[17] have stressed the incidence of arthritis ir the early diagnosis. A majority of this writer's series of connective tissue diseases has been ushered in with symptoms that suggested a diagnosis of arthritis. The purpose of the present discussion is to clarify and to document the evidence in support of the joint manifestations as they develop in the four unusual connective tissue diseases, namely, systemic lupus erythematosus, polyarteritis, acute dermatomyositis and systemic scleroderma.

HISTORICAL SURVEY

Klemperer[21] introduced the term "diffuse collagen diseases" to describe a group of conditions characterized by morphologic changes in the connective tissue. He first applied the term to acute disseminated lupus erythematosus and generalized scleroderma. Later, he added dermatomyositis. Since that time, other diseases that include polyarteritis, acute rheumatic fever, rheumatoid arthritis and serum sickness have been added. Some investigators have gone further and added such diverse maladies as glomerulonephritis, erythema nodosum, erythema multiforme, malignant hypertension, and others. Clough,[8] in an editorial, warns that the term has come to serve as a diagnostic "catch-all" for obscure and bizarre cases. He believes it has encouraged loose thinking and superficial diagnostic investigation. Further, he notes that the inclusion of so many diverse diseases has robbed the term of its diagnostic significance. Most of the early reports mention articular symptoms but, as Friedman[12] points out, scant attention has been paid to the joint manifestations, compared to various other aspects of the connective tissue diseases. Ophulus,[37] in 1923, suggested the relationship of periarteritis nodosa to rheumatic diseases because of the history of frequent bouts of "rheumatism." Baehr,[1] speaking of "a diffuse disease of peripheral circulation usually associated with lupus erythematosus and endocarditis," stated that 17 of 23 cases had joint involvement. In 1940, Slocumb[47] emphasized the similarity of the joint symptoms in lupus erythematosus and rheumatoid arthritis.

TERMINOLOGY

It is generally assumed that the term "collagen disease" has served a

good purpose, but in fact the phrase is inadequate. I believe "connective tissue" to be preferable, since the changes involved in these diseases encompass more of the connective tissue than the collagen substances. It is conceded that even this term is not completely acceptable, because other types of tissue usually are involved typically. In labeling the four unusual connective tissue diseases, we are following the usage of Talbott in his Collagen Diseases.[49]

Attempts have been made to classify the connective tissue diseases and the arthropathies that occur in them. This has led to many and varied terms. Friedman[12] speaks of the para-rheumatic arthropathies and differentiates the diseases as (1) rheumatic—easier and more definite diagnosis with less serious prognosis, and (2) para-rheumatic—musculoarticular manifestations of the connective tissue group of more serious prognosis. This investigator divided the connective tissue groups on the basis of the following clinical manifestations: (1) myalgias and arthralgias—fibrositic type, and (2) acute and subacute polyarthritis—rheumatoid arthritis type. Sperling[48] has pointed out that the connective tissue diseases may fit into the above categories but are more often atypical. We believe that these classifications contribute little The joint manifestations of connective tissue diseases should be identified as the arthropathies that occur in association with the other disseminated findings The term "arthritis" should be reserved for the specific arthritides, such as rheumatoid arthritis, septic arthritis, gouty arthritis, etc.

PATHOLOGY

Normal connective tissue consists of cellular elements (fibroblasts), very fine fibrils bound together into bundles of coarser fibers by a "cement substance," and a ground substance with the characteristics of a gel in which the fibers are imbedded and which fills the interspaces between the cells The term collagen is usually applied to all of these extracellular constituents of the connective tissue The collagen fibers are believed to be made up chiefly of a relatively insoluble protein. The ground substance is composed of hydrophilic colloids, largely the mucopolysaccharides of hyaluronic acid. This compound is believed to be a constituent of the collagen fibers of cement substance, as well as of cartilage and other formed structures

Klinge,[22] in 1933, stated that the basic change occurring in rheumatic fever and rheumatoid arthritis is in the intercellular components of the connective tissue. This change was identified as "fibrinoid degeneration" Klemperer,[21] in grouping together the connective tissue diseases morphologically, described the changes in the intercellular substance of the connective tissue. Many factors concerning these changes are still unknown. A proliferative reaction associated with an increase in the number of fibroblasts and an in-

crease in intercellular substance occurs in some instances; in others, degenerative changes predominate. Hematoxylin and eosin stain produces a strong eosinophilic reaction when collagen becomes granular and the ground substance visible, while silver stain brings out strands of fibrin. Infiltration with leukocytes completes the picture. Thus, as observed by Talbott,[49] evidence of inflammation, proliferation and degeneration may be noted.

It is this usual morphologic change that has caused confusion regarding the connective tissue diseases. There has been too much stress upon the similarities in the pathologic picture, while insufficient attention has been given to the differences. It is true, as demonstrated by Pagel,[38] that the histopathologic lesions in polyarteritis, systemic lupus, dermatomyositis and scleroderma are similar. Yet there are many differences when the several features are considered. Many cases have been reported having two or more anatomic diagnoses, exemplified by Lerman's[26] case report, which had anatomic diagnoses of polyarteritis and rheumatoid arthritis. The characteristic changes in the connective tissues are illustrated best in lupus, particularly in the vascular and synovial systems. The connective tissue of the blood vessels suffers the major insult in polyarteritis. Muscles and skin are chiefly involved in dermatomyositis and scleroderma.

Cartilage has an increased metachromacy of the ground substance, indicating a higher content of chondroitin sulphate, while the coarse collagen fibers become more widely separated, and the mesenchymal cells divide, become swollen, with a high cytoplasmic glycogen content, and then become grouped but widely separated in the highly polymerized ground substance, which is cartilage. It is rich in orientated argyrophil fibrils resembling reticulin, except that they show little branching. Their patterning, however, is significant in relation to the shaping of cartilage. In addition, there are collagen and elastic fibers; in fibro and elastic cartilage these are in higher proportion. A joint is merely an area of connective tissue free from cells and fibers in which the ground substance, in the form of synovial fluid, consists of tissue fluids with a high content of hyaluronic acid. Bone is essentially a patterned calcification of ground substance associated with increased vascularization. There is an increase of mucopolysaccharides in the ground substance with a separation of the collagen fibers and a morphologic modification of the connective tissue cells.

The joints, unfortunately, have not been studied pathologically as extensively as the other systems. We find discrepancies in the isolated observations reported in the literature. Lowman,[29] studying muscles, nerves and synovial changes in autopsied cases of lupus, reports changes similar to those seen in rheumatoid arthritis. Bennett[4] reported the pathologic synovial changes in two untreated cases of lupus and found them to be unlike rheuma

toid arthritis. He found similar fibrin deposits in two patients with scleroderma. He also noted that the muscles in lupus may show degenerative changes similar to those seen in dermatomyositis.

CLINICAL FINDINGS

Early in the clinical history of connective tissue diseases, it may be impossible or very difficult to confirm a specific diagnosis of any of the several maladies. These are chronic illnesses characterized by remissions and exacerbations They are protean in their manifestations with a catholicity of symptoms and findings. Kampmeier[17] describes a case that exemplifies what has been reported frequently in the literature and is often seen in clinical practice. The patient which he had followed for 21 years exhibited clinical evidence of dermatomyositis, was suspected of lupus at another time, and finally was proven to have been afflicted with polyarteritis This type of case has caused some investigators to believe that possibly we are dealing with a similar disease, however, we agree with Baehr[3] that "disseminated lupus erythematosus and diffuse scleroderma have in common a similar morphologic expression, namely, fibrinoid degeneration of collagen and identical lesions of blood vessels, glomeruli, endocardium, and the serous and synovial membranes. However, they are so dissimilar clinically that they seem related neither to each other nor to rheumatic fever, rheumatoid arthritis, serum sickness, periarteritis, or thromboangiitis obliterans, in which similar collagen changes may occur as part of the pathologic process"

The joint manifestations that occur at some time in the course of most patients with the less common connective tissue diseases may be confusing If the patient is followed regularly, however, the diagnosis eventually is revealed. Recent advances, e g., the discovery of the L E cell and a clearer understanding of the pathologic picture in the skin and muscle biopsies, have helped to differentiate the several conditions

LUPUS ERYTHEMATOSUS

Systemic lupus erythematosus is a generalized disease with varied manifestations which especially involve the vascular system and synovial membranes. The etiology is unknown. From 85 to 90 per cent of the patients are females, particularly young adults.

The disease is usually characterized by prolonged, irregular fever with malaise, cachexia and periods of remission. Other clinical manifestations include a butterfly rash, aggravated by sunlight which is not invariable, and polyserositis, involving the pleura, pericardium and synovia Lymphadenopathy, splenomegaly and kidney involvement may be seen. A nonbacterial verrucous endocarditis identified as the Libman-Sachs syndrome occurs The laboratory findings include leukopenia, hematuria, albuminuria, increase in the alpha and beta fractions of globulin and electrocardiographic abnormalities The L E cell may be found in the bone marrow or blood of

most cases It may not be present constantly. When found, it is presumed to be specific, particularly with a supporting clinical picture

The joint manifestations play a more important role in lupus than in any of the other connective tissue diseases discussed here. Talbott[49] points out that the symptoms referable to the muscles and joints occupy a position that is second in clinical significance to the cutaneous manifestations. It is difficult to ascertain the exact incidence. A majority of reports which discuss the clinical findings in lupus mention the joint manifestations Reifenstein[41] reviewed 18 cases and found arthropathy in each In an exhaustive study, Slocumb[47] describes ten patients in whom joints were acutely painful and swollen with local redness and heat Coburn[10] found that 23 of his 30 cases had migratory arthritis Montgomery[31] reported a 90 per cent incidence of arthralgia in 132 cases

Early in the course of lupus, differentiation from rheumatic fever or rheumatoid arthritis is difficult Murray[32] has observed that extensive and severe joint symptoms may be present for a decade or more before a diagnosis of lupus is made. Shearn,[46] in an analysis of 34 cases, stressed the similarity of articular symptoms of lupus to acute rheumatic fever Rose and Wells[44] found that 25 per cent of their 34 cases had joint changes indistinguishable from rheumatoid arthritis However, they point out that advanced destruction of articular cartilage, as seen in rheumatoid arthritis, was not demonstrated frequently Arthritis was the most common early symptom in the series of Dubois[11] and was found initially in 34 per cent of the cases

The clinical manifestations may be divided into three groups The first and largest is the arthralgia that is severe in many cases without evidence of irreversible joint damage Montgomery[31] segregated 132 cases into three groups and observed that in the chronic group, 43 per cent had arthralgia, the subacute group had an incidence of 71 per cent, while 90 per cent of the acute group had arthralgia. In Reifenstein's[41] series, the incidence of arthralgia was as high as 90 per cent. The arthralgia which occurs in lupus is accompanied by little evidence of objective joint findings Sperling[48] noted that the joint complaints may be out of proportion to the objective findings The arthralgia may be present for several years before the diagnosis of lupus becomes evident.

Second, a subacute group is recognized with varying degrees of articular symptomatology and evidence of definite joint changes with redness, swelling, tenderness and minimal deformity. Six of the patients in Slocumb's[47] series had acute and subacute attacks of swelling, pain and redness of the joints with residual joint swelling, stiffness and pain between attacks The clinical findings are typical of early rheumatoid arthritis which involve the proximal interphalangeal joints with typical fusiform swelling, as well as the elbows, knees and ankles

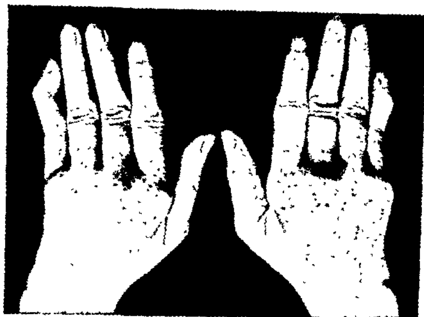


FIG 1 The hands of a patient with systemic lupus erythematosus. The appearance is similar to that of well developed rheumatoid arthritis.

Last, there is a smaller group who manifest clinically chronic deforming joint changes, many times indistinguishable from rheumatoid arthritis. Figure 1 illustrates the rheumatoid-like changes. These are the hands of a middle aged female with proved lupus Reifenstein[41] found that 30 per cent of his cases had chronic joint changes with varying degrees of deformity. One of Slocumb's[47] cases developed a chronic, deforming, progressive arthritis. In this group, the complexity of the clinical picture is enhanced by the concept of malignant rheumatoid arthritis as discussed by Ogryzlo.[34] He describes cases, as have others, of peripheral rheumatoid arthritis plus systemic symptoms plus a positive L.E. test. He has stated that the diagnosis is not lupus I disagree with his interpretation and believe that the patients died of lupus.

The following case history illustrates some of the joint manifestations and also some of the diagnostic difficulties encountered.

Case I A 39-year old white female was admitted to Memorial Hospital, Niagara Falls, New York, May 8, 1951 with chief complaints of difficulty in breathing and aches and pains in muscles and joints She had been seen previously in August 1945 for treatment of a fracture of the nose, from which she recovered without complications. Following readmission in April 1946, diagnoses of intercostal neuralgia and neurasthenia were made The next study was carried out in 1948 in a large clinic. The positive findings included slight enlargement and tenderness of the proximal interphalangeal

joints of the fingers, particularly the right middle finger The knees, elbows, an
were tender on motion but showed no other objective findings The sedimentat
was elevated The discharge diagnoses were (1) rheumatoid arthritis (mild
anxiety tension state, and (3) an irritable colon On the last admission to the h
in May 1951, bilateral pleural effusion, hematuria, mild tenderness in various
with no objective findings, elevated sedimentation rate and a positive L E cell wer
vealed The joint findings included minimal tenderness on motion particularly in
hands, wrists, knees and elbows, with no significant objective findings The postmor
examination showed involvement of the pleura, pericardium and endocardium, typ
of systemic lupus

In some instances of the connective tissue disorders, the patholog
diagnosis does not coincide with the clinical findings The following cas
history is an example of the appearance of the L.E cells in a patient with
typical rheumatoid arthritis Postmortem examination revealed a diffuse
myositis Symptoms of rheumatoid arthritis had been present for almost a
decade.

Case II * Miss I R, a 72 year-old female, presented a rather typical clinical picture of generalized rheumatoid arthritis Symptoms began first at the age of 62 The hands, wrists and elbows suffered most, although she had symptoms at times in the knees and feet. At the age of 68 she was started on a series of gold injections but developed a dermatitis and the course was interrupted Salicylates and physiotherapy resulted in some relief of symptoms The joint manifestations continued in a subacute course with slowly progressive chronic deforming changes in the upper extremities, particularly the hands

Approximately two months before the last admission to the hospital, a number of new symptoms appeared These included fever, weight loss and malaise There was no immediate explanation for this change in the clinical course A few hours before admission, symptoms suggestive of an acute abdomen developed Because of the previous demonstration of gallstones by x ray, the possibility of biliary colic or an empyema of the gallbladder was entertained On admission she was acutely ill Following surgical consultation, a localized abdominal exploration was carried out in the right upper quadrant The findings were essentially negative Because of the unexplained course of events in a patient with typical rheumatoid arthritis, the possibility of systemic lupus erythematosus was considered A search for the L.E cell phenomenon revealed many typical cells Large amounts of ACTH gel were then administered with a dramatic improvement in symptoms The patient was transformed from an apparently terminally ill person to a bright, cheerful, asymptomatic individual except for malaise As the daily dose of ACTH gel was reduced from 80 to 40 units per day her symptoms returned and an acute abdominal emergency presented itself a second time X rays of the abdomen revealed marked distension of the bowel A second limited abdominal exploration was carried out with no clear-cut findings except for the peritoneal exudate The dosage of ACTH was again increased to 80 units a day with a second dramatic improvement It was necessary to maintain the patient on this quantity of ACTH, otherwise the clinical situation regressed dramatically The patient died despite 120 units of ACTH gel daily Blood cultures on admission were sterile prior to the administration of antibiotics There were two courses of antibiotics administered without any signifi

*Included in present study through the courtesy of Dr Robert Baumler



FIG 2 Roentgenogram of the hand of a patient who suffered from well developed rheumatoid arthritis The L E cell phenomenon was demonstrated A diffuse myositis was present post mortem

cant change in the clinical course Terminally the patient died of an acute bacterial endocarditis Postmortem examination revealed a diffuse myositis but no characteristic pathologic changes of systemic lupus erythematosus, nor did the bone marrow reveal the L E cell phenomenon at this time The x rays of one hand are shown in figure 2 Characteristic changes of rheumatoid arthritis are apparent The photograph of the hands are shown in figure 3



FIG. 3 The appearance of the hand of a patient whose roentgenogram is shown in figure 2

POLYARTERITIS

Polyarteritis is a systemic disease of middle age males that affects the medium and small sized arteries. The etiology is unknown, however, Rich and others favor a hypersensitivity mechanism The course is chronic, marked by remissions and exacerbations. The catholicity of symptoms and signs represents the critical clinical feature of this disease Hypertension is present in more than 50 per cent of the cases. Gastrointestinal symptoms may be distressing and are usually located about the gallbladder or in the umbilical areas Pulmonary manifestations may vary from a simple pleuritis to a bloody effusion. It has been suggested that Loeffler's syndrome represents a mild form of polyarteritis. Cardiac involvement and pericarditis, peripheral neuritis, renal involvement and joint manifestations are common. Vascular disturbances, such as purpura, gastrointestinal hemorrhage and cerebral vascular accidents have been reported The principle laboratory findings include anemia, leukocytosis, eosinophilia, hematuria, albuminuria and occasionally nonspecific electrocardiographic changes The muscle biopsy remains the sole means of positive diagnosis The usual site for the biopsy is the gastrocnemius This is not positive in all the cases, and repeated biopsies may be necessary.

Because polyarteritis is a disease with protean manifestations of muscle and nerve involvement, the joint manifestations have not been fully appreciated. The incidence appears to be similar or less than that reported for

lupus. Ophulus,[37] in 1923, emphasized the frequent bouts of "rheumatism" which occurred in some patients afflicted with this malady. Boyd,[6] in studying 50 patients, found that musculo-skeletal phenomena shared second place with abdominal conditions. Lowman[23] observed muscle tenderness and arthralgia in 30 out of 43 patients. Nuzum,[33] in a statistical review of 175 cases and a report of one case, calculated that peripheral neuritis, articular or periarticular pain, muscle weakness, myalgia and joint swelling occurred in 54 per cent of the total. McCall[30] observed that each of his 12 cases experienced arthralgia. Jones[16] noted arthritis in 57 per cent and myalgia in 64 per cent of his series Lowman[23] and Nuzum[33] emphasize the fact that the muscle and joint involvement occurs early in the disease, often as a presenting symptom As in lupus, it is in the early phase of the disease that it is difficult to differentiate polyarteritis from either acute rheumatic fever or rheumatoid arthritis. Sperling[45] notes that as the disease progresses the joint manifestations appear to become less prominent. It may be that because of the protean manifestations in other systems, which in many patients are more dramatic, the articular symptoms and findings are minimized or overlooked Talbott[49] as well as Lowman[23] call attention to the fact that the joint findings may be migratory

The most common musculo-skeletal symptom is myalgia, which varies in degree and occurs early in the clinical course of the disease. The myalgia appears to be diffuse and may or may not be accompanied by an arthralgia. The arthropathy may be divided into three groups. The first and most frequent is an arthralgia without apparent joint changes. Typical of the incidence is found in the series of McCall,[30] who found that in each of the 12 cases arthralgia or myalgia was noted, but only two had joint swelling. Second, and not as frequent as in lupus, is a subacute group with articular symptoms which usually outweigh the joint findings Talbott[49] points out that residual stiffness, swelling and pain may be expected as in rheumatoid arthritis. Proximal joint involvement in the hands with atrophy of interossei muscles and muscles of the thenar and hypothenar eminences have been seen. The knees, wrists and elbows may also be involved Lastly, there occurs a small but definite group characterized by progressive joint changes, indistinguishable from rheumatoid arthritis. Friedman[12] observed a patient with chronic deforming joint changes which were similar to rheumatoid arthritis.

There is a serious deficiency of pathologic findings in articular structures of patients suffering from polyarteritis, although volumes have been written about the other systems. Lowman[23] reports that synovial biopsies have revealed typical polyarteritis changes in some instances. The following case illustrates not only some of the joint manifestations but the protean nature of polyarteritis

Case III A 42 year-old white male entered Mount St Mary's Hospital, Niagara Falls, New York, June 1951 with the chief complaint of recurrent bloody sputum, frothy in nature Shortly after, a segmental lobectomy was performed, the pathologic diagnosis was a simple lung cyst Aches and pains in the various joints, particularly the ankles, knees and wrists developed in August 1951 There was definite redness and swelling in a knee joint. A tentative diagnosis of rheumatoid arthritis seemed justified Not long after, purpura developed on the lower extremities Yet a third diagnosis of nonthrombocytopenic purpura was entertained at this time The patient was seen first in February 1952 with complaints of aches and pains, particularly in the joints of the lower extremities There was moderate tenderness on motion of the knees and ankles, however, without redness or swelling Purpura over both legs, bloody sputum and hematuria were observed also. A diagnosis of polyarteritis was confirmed by a biopsy of the gastrocnemius muscle In the next four years recurrent aches and pains, mild to severe, developed Occasionally, minimal swelling could be detected The joints involved were the knees, ankles and elbows He also developed a left orchitis superimposed on testicular hemorrhage, pneumonitis, transitory hypertension, peripheral neuritis and foot drop, laryngeal palsy and cerebral thrombosis with hemiplegia Spells of semi coma without an adequate explanation were observed In April 1956 severe headaches and papilledema appeared A ventriculogram was performed and a space filling defect was considered At surgery, a marked increase in intracranial pressure was the only significant finding At various times a mild or severe anemia with normal or increased white blood cell counts and a constant elevation of the sedimentation rate were noted Platelet counts were normal Albuminuria and hematuria were observed repeatedly Roentgenograms of the chest showed recurring cystlike areas. The electrocardiograms revealed minimal myocardial changes He died May 1956 An autopsy confirmed the diagnosis of polyarteritis.

ACUTE DERMATOMYOSITIS

Acute dermatomyositis is a systemic disease characterized by a nonsuppurative inflammation, usually chronic but occasionally acute or subacute, which involves the skin, skeletal muscles and occasional visceral organs The etiology is unknown; however, the frequency with which a neoplasm has been found in conjunction with dermatomyositis has caused speculation The disease usually afflicts adults between the ages of 20 and 40, with no particular sex preference. The clinical manifestations are varied The course is insidious, marked by fever and malaise with exacerbations and remissions The affected skeletal muscles may be firm and boggy and they are usually tender to superficial and deep palpation. Arthralgias are frequent, joint deformities and muscle contractures secondary to skeletal atrophy are seen. The cutaneous manifestations may be prominent or transitory Edema is relatively frequent, especially about the eyes. Transient dysphagia, abdominal cramps, weakness of sphincter and facial muscles, generalized adenopathy and splenomegaly have been reported The important laboratory findings are creatinuria, an elevated sedimentation rate, a transient eosinophilia, occasional albuminuria and a positive skin and muscle biopsy

The joint manifestations in dermatomyositis play a secondary role to

the muscular symptoms and findings Keil[18] has emphasized the lack of clinical evidence of true involvement of joints in dermatomyositis. This point of view is at variance with other observers. Clein[8] reported that the swelling of proximal phalangeal joints, subluxation and ulnar deviation leaves little doubt regarding a presumptive diagnosis of *rheumatoid arthritis in selected* instances of acute dermatomyositis Anderson[1] believes that the joint process is indistinguishable from rheumatoid arthritis.

It is difficult to ascertain the incidence of arthropathy in dermatomyositis Jager[15] reported that muscle involvement was present in each of the nine cases of his series. Only three patients had articular symptoms without swelling of joints. O'Leary[36] believes that only 5 per cent of the patients have true articular involvement even though the stiffness and pain on motion often causes a mistaken diagnosis of arthritis. Ragan,[39] in a study of 25 cases, reported that seven had joint stiffness and periarticular swelling Three of his cases had findings characteristic of rheumatoid arthritis Again, it is early in the course of the disease that a mistaken diagnosis of arthritis is usually made. Kellogg[19] has described an interesting patient who had a bout of migratory polyarthritis six years before the clinical picture of dermatomyositis *was entertained A clinical diagnosis of mitral stenosis was also made* in this patient.

The musculo-skeletal symptoms and findings consist chiefly of muscle tenderness and weakness The muscle atrophy which occurs may be advanced, with extensive fibrosis and contractures of large and small joints, notably the elbows, knees, digits and wrists. The arthropathy has been divided into three groups. Arthralgias, without any significant joint findings, are fairly common, particularly early in the disease. The second group consists of a small number of patients who have symptoms of pain in the same joints involved as in rheumatoid arthritis. The swelling and redness noted in these joints are minimal. Finally, there are selected instances in which a chronic, *deforming* arthritis, indistinguishable from rheumatoid arthritis, may be observed. Examples of the last two groups are seen infrequently.

The following case illustrates the musculo-skeletal phenomena in acute *dermatomyositis The joint symptoms may be described best as* arthralgia.

Case IV A 39-year-old female entered Memorial Hospital, Niagara Falls, New York, June 1955 with the chief complaints of a skin rash and aches and pains The skin manifestations *had been present for two years For one year she had complained* of diffuse muscle aching of varying severity Physical examination revealed that the skin lesions consisted of confluent erythematous macular patches with edema on the forehead, neck, upper arms and anterior chest A dermatologist stated that the lesions were consistent with either dermatomyositis or lupus. There was tenderness to mild and deep palpation, particularly of the muscles of the upper arm and back. There was no joint swelling or redness There was some tenderness on motion of the elbows, wrists and fingers of the hands The sedimentation rate was *elevated A skin and muscle biopsy* of the deltoid area showed changes consistent with acute dermatomyositis

SYSTEMIC SCLERODERMA

Systemic scleroderma is a generalized disease manifested by changes in the skin, subcutaneous tissues and various visceral organs. The etiology is unknown. This condition occurs more commonly in females and usually appears in the middle decades of life. The disease is progressive with minimal *evidence of remissions. The striking clinical manifestation is the involvement* of the skin. This progresses through several stages from a brawny edema to a smooth, tight, waxy skin under which the subcutaneous and muscle tissues become atrophied. Any area of the skin may be involved but the disease usually begins in the extremities, the bridge of the nose, cheeks, forehead and the anterior portion of the chest. Indolent ulcers are observed, particularly at the fingertips Marked limitation of motion or ankylosis of joints may develop, secondary to the sclerodermal changes of the skin Calcinosis circumscripta or universalis is not unusual Raynaud's phenomena usually appear early in the course of the malady. Arthralgia may be troublesome Dysphagia secondary to esophageal involvement, dyspnea and cyanosis secondary to pulmonary involvement, heart block and cardiac failure have been reported. A skin biopsy is the only means of positive diagnosis in the early stages of the disease.

Of the four connective tissue diseases discussed in this study, systemic scleroderma has the least information available in the literature relating to the arthropathy. Talbott[49] has stated that the incidence of arthralgia or symptoms suggestive of rheumatoid arthritis is considerably lower than in patients with lupus or dermatomyositis. Early in the course of scleroderma the arthropathy appears to play an important part O'Leary[35] found that arthritic symptoms were noted initially in 28 of 48 cases. Ramsey[40] and Richter[43] have reported that a suspicion of rheumatoid arthritis has been entertained in some patients with scleroderma in the early months of the disease. Lewis[27] points out that the onset of scleroderma is insidious and may appear as an arthralgia Leinwand,[25] in a study of over 150 cases observed that pain in the joints almost always is present and may precede any apparent skin changes. Each of the six cases in our study had had a presumptive diagnosis of arthritis entertained early in the disease The musculo-skeletal manifestations of scleroderma, therefore, appear to be those as a result of skin changes There is tightness and stiffness of the skin, in and about the joints, progressing to limitation of motion or ankylosis of the joints.

The arthropathy in scleroderma can be divided into two parts First, there is the arthralgia which occurs early in the disease and varies from slight pain and swelling to severe pain with swelling and stiffness of the joints. It must be noted that arthralgia with minimal joint manifestations is most common. Second, the arthropathy appears as contractures and deform-

ities of the joints suggestive of rheumatoid arthritis. However, this is usually secondary to the sclerodermatous skin changes. It is interesting to note that in a study by Boyd,[5] in which roentgen changes were observed in systemic scleroderma, 17 of 31 patients showed changes suggesting the diagnosis of *rheumatoid arthritis.*

The following case is illustrative. Early differentiation from arthritis was difficult. As the disease progresses, *the skin findings may be so sufficiently* typical that the correct diagnosis is mandatory.

Case V A 31-year-old white female entered Mount St. Mary's Hospital, Niagara Falls, New York, September 1950 with complaints of generalized pains, particularly in the extremities She had been seen first by a physician in November 1949, at which time a *diagnosis of rheumatoid arthritis had been suggested. However, because of the* pigmentation of the skin on the anterior chest and face, systemic lupus was suspected Electrocardiographic changes suggestive of pericarditis were reported She was treated *with steroids When seen by this writer, the skin* was tight and indurated over the exposed portions of the hands and face. An acne, presumed to be due to steroids, was present The joints of the extremities were stiff with minimal limitation of motion They were particularly tender on motion. There was no significant swelling in the joints. The clinical course was rapidly progressive with increasing firmness of the skin and limitation of motion of the joints of the upper and lower extremities Systemic manifestations included gastric symptoms The roentgens of the esophagus were reported as follows: "The esophagus is slightly dilated and at the time of fluorscopic examination no peristalsis was evident. Barium passed readily into the stomach, however No peristalsis is evident on the films. The changes are consistent with scleroderma" The patient died in January 1952

This following case report demonstrates particularly the similarity in the roentgen changes of the joints (fig 4).

Case VI Mrs. E H, a 69-year-old housewife, suffered from Raynaud's phenomenon of the fingers for more than 20 years She also complained of "arthritis" which was believed to be caused by chronic progressive changes in the skin of the fingers from *scleroderma, rather than from typical rheumatoid arthritis A number of months before* she was admitted to the hospital, gangrene of three of the terminal phalanges appeared. It was accompanied by excruciating pain She had increasing shortness of breath, although she had been able to carry on her household duties as a housewife on a farm It was difficult to obtain a history of any well developed gastrointestinal symptoms, although she complained of some difficulty in swallowing, gas and two episodes of vomiting On physical examination the chronic changes of advanced scleroderma of the hands and face were apparent There was a reddish violet macular papular rash on the face and over the bridge of the nose There was dry gangrene of three of the terminal phalanges There were a number of "spiders" and areas of telangiectasia. The various laboratory studies included 4+ cephalin flocculation, a serum albumin of 3 4 Gm. and serum globulin 3.8 Gm, a maximum breathing capacity of 65 per cent normal, diffuse fibrosis of both bases of the lungs by x ray and enlargement of the heart Roentgenographic study of the small bowel showed pooling of the barium in *the lower esophagus* and irregular segmentation of the lower ileum, consistent with the findings sometimes observed in patients with scleroderma The bromsulphalein retention was 25 per cent. The patient was placed on 12.5 mg *of prednisolone and responded well with a gain in weight* and subsidence of pain in the digits.

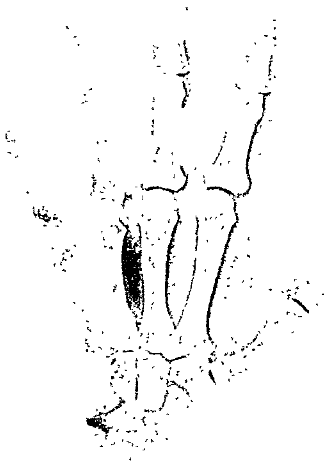


FIG. 4 Roentgenogram of the [illegible] [illegible]ferre[illegible] [illegible]emic scleroderma for many years. [illegible] [illegible]anges is apparent.

An attempt has [illegible] the four unusual [illegible] tosus, polyarteri[illegible]

view of the clinical findings and illustrations of each malady have been pr sented. The similarity of the clinical findings of the arthropathy in thes diseases to those of rheumatic fever or rheumatoid arthritis has been di cussed. The possibility of one of the unusual connective tissue diseases shoul be entertained in any patient suffering from what appears to be one of th more common maladies.

References

1 Anderson, T E Dermatomyositis. Brit J. Derm 64 71, 1952

2 Baehr, G, Klemperer, P and Schrifrin, A · A diffuse disease of the peripheral cir culation (usually associated with lupus erythematosus and endocarditis). Tr A Am Physicians 50. 139, 1935

3 Baehr, G, and Pollack, A. D Disseminated lupus erythematosus and diffuse sclero derma J A M A 134 1169, 1947

4 Bennett, G A and Dallenbach, F D Synovial membrane changes in disseminated lupus erythematosus, observations of two autopsied cases. Mil. Surgeon 109. 531, 1951

5 Boyd, J A Patrick, S. I and Reeves, R J.: Roentgen changes observed in generalized scleroderma, report of 63 cases Arch Int Med. 94: 248, 1954

6 Boyd, L. J The clinical aspects of periarteritis nodosa Bull New York M Coll 3 32, 1940

7 Brock, W G. Dermatomyositis and diffuse scleroderma; differential diagnosis and reports of cases Arch Derm & Syph. 30 227, 1934

8 Clein, L.· Acute dermatomyositis Brit M J 2 1357, 1953

9 Clough, P. W Editorial Collagen Diseases Ann Int Med 42: 213, 1955

10 Coburn, A F and Moore, D H · The plasma proteins in disseminated lupus erythematosus, Bull Johns Hopkins Hosp. 73· 196, 1943

11 Dubois, E. L. The effect of the L. E. cell test on the clinical picture of systemic lupus erythematosus Ann Int Med 38. 1265, 1953.

12 Friedman, H H, Schwartz, S, Trubek, M and Steinbrocker, O The "Para Rheumatic" Arthropathies Ann Int Med 38 732, 1953

13 Harvey, A McG., Schulman, L. E, Tumulty, P. A., Conley, C. L. and Schroenrich, E H - Systemic lupus erythematosus; review of the literature and clinical analysis of 138 cases Medicine 33 291, 1954

14 Haserick, J R · Modern concepts of systemic lupus erythematosus J Chronic Dis 1 317, 1955

15 Jager, B V. and Grossman, L V · Dermatomyositis Arch Int Med. 73 271, 1944

16 Jones, G M., Jr.,· Periarteritis nodosa with case reports. Ann Int. Med 16. 920, 1942.

17 Kampmeier, R H and Shapiro, J L Diffuse and sometimes recurrent course of diffuse arteritis; observations and report of a patient observed for twenty-one years Arch Int Med 92. 856, 1953

18 Keil, H · Dermatomyositis and systemic lupus erythematosus. II A comparative study of the clinicopathological features 66· 339, 1940

19 Kellogg, F. and Cunha, F: Dermatomyositis, report of a case associated with rheumatic heart disease California & Western Med 50 337, 1939

20 Kinney, T D and Maher, M M Dermatomyositis, study of five cases Am J Path 16, 561, 1940

21 Klemperer, P., Pollack, A D and Baehr, G Diffuse collagen disease, acute disseminated lupus erythematosus and diffuse scleroderma J A M A 119 331 1942

22 Klinge, F Der Rheumatismus Pathologisch-anatomische und experimentell pathologische Tatsachen und ihre Auswertung für das ärztliche Rheuma problem Ergebn d allg Path U path Anat 27 1, 1933

23 Knowles, J C., Jr., Zeek, P M and Blankenhorn M A Studies on necrotizing angiitis i v periarteritis nodosa and hypersensitivity angiitis Arch Int Med 92 789, 1953

24 Langmead, F S The relationship between certain rare diseases generalized scleroderma, calcinosis, dermatomyositis, myositis fibrosa Arch Pediat 40 112 1923

25 Leinwand, I., Duryee, A W and Richter, M N Scleroderma (based on a study of over 150 cases) Ann Int Med 41 1003 1954

26 Lerman, J and Bauer, W Massachusetts General Hospital case report New England J Med 243 1003, 1950

27 Lewis, T and Landis, E M Further observations upon a variety of Raynaud's disease, with special reference to arteriolar defects and to scleroderma Heart 15 329, 1929 31

28 Lowman, E W: Joint and neuromuscular manifestations of periarteritis nodosa Ann Rheum Dis 11 146, 1952

29 Lowman, E. W: Muscle, nerve and synovial changes in lupus erythematosus Ann Rheum Dis 10 16, 1951

30 McCall, M and Pennock, J W Periarteritis nodosa, our present knowledge of the disease Ann Int Med 21 628, 1944

31 Montgomery, H and McCreight, W G Disseminated lupus erythematosus Arch Derm & Syph 60 356, 1949

32 Murray, M J Chronic disseminated lupus erythematosus Proc Roy Soc Med 41 922, 1951

33 Nuzum, J W, Jr and Nuzum, J W, Sr Polyarteritis nodosa, statistical review of one hundred seventy-five cases from the literature and report of a 'typical' case Arch Int Med 94 942, 1954

34 Ogryzlo, M A Diffuse systemic rheumatoid arthritis Ann Rheum Dis 12 323, 1953

35 O'Leary, P A and Norland, K A clinical study of one hundred and three cases of scleroderma Am J M Sc 180 95 1930

36 O'Leary, P A and Waisman M Dermatomyositis, a study of forty cases Arch Derm & Syph 41 1001, 1940

37 Ophüls, W Periarteritis acuta nodosa Arch Int Med 32 80 1923

38 Pagel, W., Woolf, A L. and Asher, R Histological observations on dermatomyositis J Path & Bact 61 403, 1949

39 Ragan, C. The effect of adrenotropic hormone (ACTH) (Armour) on the clinical syndrome of dermatomyositis. Proc First Clinical ACTH Conf., Philadelphia The Blakiston Co., 1950 (p 423)

40 Ramsey, A S.: Acrosclerosis Brit M J 2 877 1951

41 Reifenstein, E. C., Reifenstein, E. C., Jr. and Reifenstein, G. H.: A variable symp tom-complex of undetermined etiology with fatal termination. Arch. Int. Med *63*: 553, 1939
42 Rich, A R. and Gregory, J E: Experimental evidence that lesions with the basic characteristics of rheumatic carditis can result from anaphylactic hypersensitivity. Bull Johns Hopkins Hosp *73* 239, 1943
43 Richter, R B. Peripheral neuropathy and connective tissue disease. J Neuropath & Exper Neurol *13*. 169, 1954
44 Ross, S W and Wells, B. B.: Systemic lupus erythematosus; a review of the literature. J Clin Path *23*· 139, 1953.
45 Sheard, C., Jr Dermatomyositis Arch Int. Med. *88*. 640, 1951
46 Shearn, M. A and Pirofsky, B. Disseminated lupus erythematosus, analysis of thirty-four cases Arch Int Med *90* 790, 1952
47. Slocumb, C. H Arthralgia and arthritis of lupus erythematosus Proc. Staff Meet., Mayo Clin *15*· 683, 1940
48 Sperling, I L Joint manifestations of the collagen diseases J. M Soc. New Jersey *51* 251, 1954
49 Talbott, J H and Ferrandis, R M Collagen Diseases New York, Grune & Stratton, 1956

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